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A STRIKING ELEVATION OF THE TEMPERATURE OF THE HAND AND FOREARM FOLLOWING THE EXCISION OF A SUBCLAVIAN ANEURISM AND LIGATIONS OF THE LEFT SUBCLAVIAN AND AXILLARY ARTERIES

By William S. Halsted

In a series of signally interesting papers Professor René Leriche calls attention to the value of what he terms peri-arterial sympathectomy in the treatment of various neuralgias, local ischemias, reflex contractures of the Babinski-Froment type, and other affections. Fostered in the traditions of the schools of Magendie, Claude Bernard, and Brown Séquard, it was in the happy order of things that it should fall to the lot of a surgeon of Lyon to turn to therapeutic account a discovery of the greatest of the founders of experimental medicine. A devoted disciple of Jaboulay, Leriche credits this talented surgeon, his "master," with the suggestion which led to the novel and important researches made by him during the years of the war.

My interest in Leriche's work has been reawakened by an observation made only a few weeks ago in the Surgical Clinic of The Johns Hopkins University. In 1918 I ligated the left subclavian and carotid arteries near their origin from the aorta for the cure of a huge subclavian aneurism (Figs. 1 and 2). For a year the aneurism decreased steadily in size (Figs. 3, 4, 5 and 6). Then for a year we lost track of the patient. About two months ago we succeeded in tracing him, and persuaded him to let us excise the aneurism, which in the period of non-observation had developed a faint pulsation and become slightly larger (Fig. 7). About four hours after this operation, at which the aneurism was excised and the subclavian and axillary arteries ligated, it was noticed that the left hand and forearm, which for two years had been strikingly cold, had become abnormally warm—appreciably warmer than the corresponding limb. Unfortunately, our surface thermometer had been broken and we were unable to obtain another. About five weeks after the operation the hand and forearm became cold again—at first in small areas—remaining cold for only a day or two.

To-day (June 28) the 69th since the operation, the back of the left hand is quite cold, whereas the left palm is about as warm as the right. The temperature of the hand and forearm has varied from day to day and from hour to hour; certain small, quite well-defined areas have remained uniformly cool; otherwise, the hand and forearm have maintained their normal warmth.

Sur. No. 46179. Alexander Miller. Negro, æt. 29. Admitted to The Johns Hopkins Hospital April 22, 1918; discharged August 12, 1918.

The patient states that he has always been perfectly well. In April, 1917, he noticed a swelling about the size of an egg above

the left clavicle. Almost simultaneously with the recognition of the swelling, pain and numbness in the upper extremity were observed. The growth of the tumor was gradual until about March, 1918; since then it has been very rapid. For the past two weeks the limb has been totally paralyzed. The patient recalls that until Christmas, 1917, he could still raise his arm a little.

About four years before admission the patient was shot just above the left clavicle. The wound healed promptly. The bullet was not removed and has given him no indication of its presence.

Examination.—The patient is evidently suffering severe pain, and constantly supports his left wrist with his right hand. The pain, he says, is most intense from the elbow-joint to the hand and in the left shoulder.

A huge aneurism occupies the left neck from the clavicle to the ear (Figs. 1 and 2). The head is deflected and rotated to the right. The vertex of the pulsating mass is about on a plumb-line dropped to the junction of the middle and inner thirds of the clavicle. The swelling and pulsation extend on to the chest, and the whole body is jarred with each heartbeat. Posteriorly the diffuse pulsating tumefaction spreads out to a point below the spine of the scapula. The aneurism extends upward in dome-shape; a hand can be inserted between it and the face down to the angle of the lower jaw. The whole shoulder girdle appears to be raised away from the chest wall, the acromio-clavicular articulation being apparently disrupted. The skin over the tumor is very tense and glistening. From the clavicle to about the level of the nipple the brawny tissues are probably infiltrated with blood as well as inflammatory products. The trachea is displaced to the right. A systolic bruit, most distinct above the inner third of the clavicle, can be heard over the greater part of the pulsating mass. No thrill can be felt. The left radial pulse is absent. There is slight ptosis of the left eyelid, but the pupils respond equally. Only the inner third and the acromial tip of the clavicle can be defined with the fingers. The remainder of the bone is buried in the tumefaction. A bullet is palpable just beneath the skin to the left and below the spine of the seventh cervical vertebra. The left arm is paralyzed. The extent of the loss of motion and sensation and the degree of restoration of function will be outlined in a subsequent paper.

Fluoroscopic Examination.—The shadow of the aneurism extends to the lower border of the clavicle but not to the first rib. The heart seems not to be enlarged. The right subclavian and carotid arteries, distinctly seen, are normal in size.

Skiagraphic Report.—Large mass in left neck. Clavicle deeply eroded, perhaps fragmented. Bullet in upper dorsal region.

Operation.—April 26, 1918. Dr. Halsted. *Ligation of the left common carotid and the left subclavian arteries near their origin from the aorta.*

Ether. Wide protection of the operative field with celloidin-silk.[1] Transverse bow-incision just below the cervico-thoracic junction, supplemented by a vertical one along the left border of the sternum (bow and plummet incision). Free exposure of manubrium and left sterno-clavicular joint. The incised tissues were œdematous, particularly so below the clavicle. The superficial vessels were abnormally large. Careful hemostasis by the fine silk transfixion method. The left two-thirds of the manubrium and the left sterno-clavicular joint were resected with the giant rongeur forceps of Esmarch, care being taken to avoid disturbing the fragments of the eroded clavicle. The thymus gland and the left innominate vein were drawn upward and to the right with a retractor.

The trachea in the thorax as well as in the neck was displaced to the right by the pressure of the aneurism. The left carotid, deeply situated and occupying the midline in the chest, was gently occluded with a tape ligature. This artery was thought at first to be the left subclavian inasmuch as, according to the erroneous testimony of an assistant, its occlusion did not affect the pulse in the left temporal artery, and lessened the force of the pulsation in the aneurism. To obtain access to the left subclavian artery the cartilage of the left first rib and the adjoining margin of the sternum were cut away. The arch, the aortic isthmus and descending aorta, and the left auricle of the heart were palpated with the finger of the operator before the left subclavian, lying close to the vertebral column, was identified. With the aid of four long, narrow dissectors, two of which were manipulated by the operator and two by Dr. Mont Reid, the vessel was clearly exposed at its origin from the aorta and for several centimeters distal to this point. As it was evident that none of the various aneurism needles was suitable for the passage of a ligature at this depth, a long, narrow, blunt dissector, slightly curved and pierced at its tip, was armed with fine silk and passed under the artery. By means of this thread and then another, linen tapes were drawn under the subclavian; both of these were tied, the second distal and close to the first, with force only sufficient to close completely the artery's lumen. The aneurism became very tense and hard immediately after the ligation, but was pulseless.

The patient's condition, bad on admission and particularly so just before operation, caused us some anxiety. Traction within the thorax on the branches of the aortic arch or on the pulmonary artery affects unfavorably and eventually disastrously the action of the heart. The pulse, about 120 at the beginning, was 140+ and quite weak at the termination of the operation. The wound was completely and accurately closed with interrupted sutures of fine silk. A large dead space in the mediastinum was, naturally, unavoidable.

Healing *per primam.*

November 9, 1918. The patient has been examined frequently since his discharge from the hospital. There has been no pulsation in the aneurism since the operation. The mass has steadily but slowly decreased in size. The patient can make slight movements with the left fingers, otherwise there has been no appreciable return of power or sensation in the paralyzed arm.

The patient was observed frequently throughout the year following the operation. Slowly but steadily the pulseless tumor, during this period, diminished in size. Then for a year the patient, living out of town, was lost sight of. Exactly two years after the first operation he returned, at our solicitation, to the hospital. Now for the first time since the operation a very faint pulsation was discernible. The tumor (Fig. 7) measured in its transverse (frontal) diameter precisely the same as when last seen a year before; the antero-posterior measurement (sagittal), however, gave an increase of about 4 c. m. I decided that the aneurism should be excised, and on the 20th of April, 1920, performed the operation as follows:

The skin over the tumor and a wide area about it were protected with Chinese silk dipped in celloidin. The incision, made through the tightly adherent silk, ran with the clavicle in its central part, curving up into the neck at its inner end, and down along the cephalic vein at its outer. Superimposed on and not attached to the greatly broadened and thickened clavicle was a sharply convex bow of bone about 9 cm. long and 6 mm. thick. This bow, recognizable in the photograph (Fig. 5), was cut away and the clavicle bitten through with a heavy rongeur forceps at two points as close to the aneurism as possible. The cephalic vein was divided, and the axillary artery—pulseless, reduced in

[1] W. S. Halsted. Clinical and Experimental Contributions to the Surgery of the Thorax. Trans. Amer. Surg. Assn., 1909, xxvii, p. 111.

FIG. 1.—Aneurism of the left subclavian artery, Alexander Miller, April 22, 1918.

FIG. 2.—Alexander Miller, April 22, 1918.

FIG. 3.—Alexander Miller, 109 days after ligation of the subclavian artery near its origin.

FIG. 4.—Alexander Miller, 109 days after the ligation.

FIG. 5.—Alexander Miller, 10 months after the ligation.

FIG. 6.—Alexander Miller, 10 months after the ligation.

FIG. 7.—Alexander Miller, 2 years after the ligation of the subclavian, and 2 weeks before the excision of the aneurism.

FIG. 8.—Alexander Miller, 1 month after excision of the aneurism.

size, but not empty—was ligated about at the junction of its first and second portions, through a split made in the pectoralis minor muscle; the third portion of the subclavian artery was ligated above the clavicle; the aneurismal sac, and the resected rib were excised in one piece. The aneurism was matted almost everywhere to the surrounding parts by dense connective tissue, and hence had to be carved out rather than enucleated. The identification and freeing of the roots of the brachial plexus, which were in places embedded in the wall of the sac, consumed much time. The operation was conducted in a bloodless manner until nothing remained to be done except to divide the narrow neck of the sac. The tissues of this neck proved to be thin and friable, and the patient lost a few cubic centimeters of blood through the slit in the artery—the mouth of the false sac—which was readily closed with three stitches of fine silk. The wound was closed without drainage. I am greatly indebted to Dr. Heuer and Dr. Reid for their skilful and highly competent assistance which enabled me without concern to conduct the operation to a satisfactory conclusion.

At the first dressing, made on the 10th day after operation, it was noted that a little fluid had accumulated in the outer part of the wound. This was evacuated by puncture with a wooden toothpick wrapped with a few fibres of cotton dipped in pure carbolic acid. Closure of the puncture was prevented by the reapplication of the acid in the same manner on two alternate days. The introduction of a drain of any kind we scrupulously avoid. The word "drainage-tube" is in disfavor in our clinic. Should a wound become infected, tubes would be properly introduced for the purpose of disinfection, but not for drainage.

Noteworthy is the fact that the patient's hand and forearm, which prior to and ever since the first operation had been markedly cold, became strikingly warm about 4 hours after the second operation and have remained warm, except in certain areas, to the present time (June 28). It is improbable that the ligation of the cephalic vein was in any part responsible for this indubitable improvement in the circulation. The elevation of the temperature of the hand and forearm must, I believe, be attributable to vasodilatation incident to the ligations of the subclavian and axillary arteries—to the crushing of their nerves. This question will be discussed in the course of the consideration of the treatment of subclavian aneurisms in a paper about to appear in The Johns Hopkins Hospital Reports.

I have found pleasure in translating one of the papers of Monsieur Leriche, believing that his work on periarterial sympathectomy will at this moment particularly interest surgeons who may have the opportunities and the inclination to verify his observations. While disclaiming unqualified acceptance of some of his explanations and deductions which are at variance with the teachings of physiologists we must recognize that Leriche's contributions are of unusual interest and value; they will stimulate investigation.

PERIARTERIAL SYMPATHECTOMY AND ITS RESULTS

RENÉ LERICHE

In January, 1916, and in April of the same year,[2] I made known the first results which the denudation and excision of the sympathetic plexuses around the arteries in causalgia and in certain trophic troubles had given me. Since then this operation has been tried in various ways. Le Fort, Cotte, Sencert, Lavenant, de Massary and Veau, Prat, have reported experiences with it. I personally have performed it 37 times.[3] The moment seems to have come to indicate briefly the essential facts which the procedure has taught me. Elaborating the idea of Jaboulay, we must indeed develop a true and general operative method susceptible of very varied applications.

I think at the outset that it ought to be designated by an exact name: it is a peripheral sympathectomy which, according to the level where it is practised, ought to be called axillary sympathectomy, brachial, iliac, femoral, etc.

I. TECHNIQUE.—In order to achieve it, it is necessary to uncover the artery by the classic procedure, open with the bistoury the cellular sheath, separate the artery for 8 to 10 cm., get hold of the inner sheath directly on the vessel wall, incise it, pull one of the lips thus made with a forceps, free it either with the bistoury or with the grooved probe, completely stripping the artery of all the cellular tissue that adheres to it. More or less easily according to the cases, one is able thus to strip the artery, to decorticate a fold; thin, to be sure, but often thicker than one might expect. At a certain moment one has the impression that one is going to tear the wall of the artery; but if one proceeds gently and carefully, guided by the point of the bistoury or probe, the freeing process can be carried on without risk of injuring the vessel. Only twice have I had the annoyance of making a small tear in the artery; the accident was without serious results. In case of necessity one would frankly resect the segment of the tear and tie the two ends, accomplishing thus by the same act a complete sympathectomy. Sometimes the forceps removes only rather short cellular fragments, at other times one removes quite definite laminæ, and the movement of freeing recalls, on a small scale, the subserous decortication of an inflamed appendix, but one never succeeds in removing a continuous layer; it is necessary to repeat the attempt several times and with perseverance to catch the sheath again, to remove thin meshes, and not to stop until one has really the feeling of having removed everything. Moreover, one can verify what has been done by wetting the wound with a tampon soaked with very warm serum: the artery takes on then a whitish appearance, looks as though made of felt, and one sees very clearly whether there remains still some cellular débris more or less detached.

In the course of the cellular decortication it is necessary to be careful to expose the collateral branches and guard against tearing them. This happens sometimes; by using then a forceps and a ligature of 00 catgut one repairs this accident without injury to the artery. In addition to the tears, which cause a spurt of pure blood, there may be oozing from the tearing of the vasa vasorum.

II. THE PHYSIOLOGICAL REACTION.—The operation thus done is a physiological operation; I mean to say by this that it is inevitably followed by a characteristic physiological reaction, which may be regarded as the *test of the operation;* as there are characteristic signs of the section of the trunk of the sympathetic in the neck, so there are characteristic signs of the section of the periarterial sympathetic nerves. If these are wanting, the operation has been attempted but not accomplished.

The results of our studies of these signs Heitz and I have reported to the Société de Biologie;[4] they are as follows:

Primary Sign.—When one touches the sympathetic sheath, the

[2] R. Leriche: De la causalgie envisagée comme une névrite du sympathetique et de son traitement par la dénudation et l'excision des plexus nerveux péri-artériels. Société de Neurologie, 6 Janvier 1916; La Presse médicale, 20 Avril 1916.

[3] More exactly, I have done 30 sympathectomies by denudation and 7 times complete sympathectomy by resection of a segment of obliterated artery.

[4] Leriche and Heitz: Des effets physiologiques de la sympathectomie périphérique (réaction thermique et hypertension locales). C. R. de la Soc. de Biol., 20 Janvier, 1917.

artery contracts; it is reduced progressively in size to the point where it is not more than a third or even a fourth the normal size throughout the whole extent of the denuded segment. The segments on both sides maintain their normal size provided the operation has not injured them. The phenomenon is more or less rapid according to the case; certain individuals appear to have more irritable sympathetic nerves than others; their arteries diminish in size at the first touch; with some the contraction is sluggish. One cannot yet give the real reason for these variations. Furthermore, the contraction is more marked in the brachial than in the axillary and the subclavian; it is slower in the femoral than in the brachial, and less intense in the common iliac than in the femoral. In a word, the contraction is stronger in the arteries of small size than in the large trunks.

This arterial contraction habitually causes the pulse to disappear, but it does not altogether interrupt the circulation.

Secondary Signs.—In the following hours the pulse is imperceptible or very feeble and the limb is colder than the other. Then little by little, at the end of three hours, six hours, and most often after twelve or fifteen hours there appears the *characteristic physiological reaction*, the establishing of which ought to be exacted as proof that suppression of the sympathetic nerves has been properly done.

This reaction is characterized by an elevation of the local temperature reaching to 2° and even 3° [centigrade], by the elevation of the arterial pressure, and by the augmentation in the amplitude of the oscillations of Pachon. M. Heitz, who with his very special competence has established these facts many times on my patients, has found that the increase in pressure could be as much as 4 cm. of mercury in comparison with the healthy side (method of Riva Rocci); it is a detail worthy of mention that analogous figures were noted by Claude Bernard in his investigations of the cervical sympathetic nerves.

This vasodilator reaction is only temporary: the hyperthermia, the rise in pressure, and the increase in amplitude of the oscillations diminish little by little; sometimes as early as the 15th day and usually at the end of a month one finds it no more. On the other hand, in some cases in which I have performed sympathectomy on the brachial or the subclavian artery by resecting totally the obliterated arterial cord, the elevations of temperature have been more lasting than in the cases in which a sympathectomy by denudation alone was done. This is comprehensible, for the operation is more complete—the sympathectomy being necessarily total. Classed with these observations should be one made by M. Babinski and M. Heitz: four months after the extirpation of an axillary aneurism the hand on the side operated on was frequently warmer than that on the healthy side. This phenomenon, apparently paradoxical, is understood very well when one considers that the ablation of a sac is in reality a total sympathectomy.

III. The Lessons Furnished by the Operation.—Observation of series of operations and analysis of the therapeutic results permit interesting deductions from physiological and pathological points of view.

1. *From the Physiological Point of View.*—Two facts become clear: the vasomotor phenomena which Heitz and I have studied under the name of vasodilator reaction permit us to isolate the paths along which certain vasoconstrictive acts are conducted and to establish their correct value.

But there is, above all, this one: it seems to follow from certain observations that the voluntary muscular contraction is, in a certain sense, very dependent on the sympathetic nerves. The integrity of the motor nerve and of the muscle are not sufficient to insure the proper accomplishment of the movement that is commanded. If the sympathetic nerve is affected at a distance or if it does not act normally, the muscle becomes hard, and contracts, and the will is powerless to relax or contract it. Now in these cases sympathectomy lifts the barrier and makes possible the progressive reparation of the voluntary movements. In the case of wounded men having reflex contractions of the Babinski-Froment type, with fingers twisted, motionless, incapable of movement, it has been sufficient to modify the vasomotor innervation to see a certain degree of voluntary motion appear again the following day.

This fact which M. Heitz[5] and I have confirmed several times has a real physiological bearing. What we now know of muscle innervation in man does not lead us to suppose that it is a matter of a directly muscular action. It appears, until we have made further inquiry, that the vasomotor phenomena alone are concerned in it, and a fact which would tend to prove this is that the return of motility coincides with the appearance of the post-operative vasodilator reaction (that is to say, the warming up of the muscle, its new circulatory system), and follows the course of it.

Sympathectomy, furthermore, would appear to establish the fact that the sympathetic nerve is, in man, the excitosecretory nerve of the sweat glands; I have seen profuse sweating of the hand disappear after sympathectomy. The nerve probably also influences the growth of the nails and the trophicity of the skin, since trophic phenomena disappear rapidly after sympathectomy. The nerves of the cerebrospinal system, from this point of view, are probably only the vectors of the sympathetic.

2. *From the Point of View of Pathological Physiology.*—Sympathectomy is, in certain cases, a true method of experimental analysis for the interpretation of certain complex phenomena.

It demonstrates: (a) *The true mechanism of the production of dry wounds of the arteries.* Spontaneous hemostasis, when an artery is divided or destroyed by a projectile, is certainly greatly facilitated by, if it is not entirely due to, the contraction of the artery which follows the destruction of its sympathetic nerve. It may be compared to the considerable diminution of calibre which is observed after sympathectomy. Since a brachial artery is reduced to the size of a radio-palmar or a digital when its sympathetic nerve is excised, it is easy to comprehend how spontaneous hemostasis is possible after certain wounds of the arteries which are inevitably accompanied by tearing of the sheath.

(b) *The real nature of certain causalgias, if not of all.* As I demonstrated to the Société de Neurologie, in January, 1916, one can cure obstinate causalgias by excising the involved sympathetic nerve. This observation proves the sympathetic origin of the violent pains which accompany certain wounds of nerves. In these cases the pain phenomena are not due to the nerve lesions, but to the lesions of the neighboring sympathetic nerve (the perivascular sympathetic of the brachial) or of the intra-nerve sympathetic (the sympathetic carried to the median, for example, by its particular artery). This explains the fact demonstrated by M. Pierre Marie, M. Miege and Mme. Bénisty that the pain in these nerve wounds is a kind of reaction peculiar to the nerves which have an artery of their own or which are close to a large artery. This fact is now admitted by the neurologists.

(c) *The very great rôle of the sympathetic in the production of the reflex contractions of Babinski-Froment.* Let us pay attention to the characteristics of this type about which there is so much confusion. I speak now of the true Babinski-Froment type, that in which the vasomotor and thermic phenomena are associated with motor disturbances and with modifications of the mechanical excitability of the muscles.

In the cases of this kind, studied by M. Babinski or by his assistants Froment and Heitz, I have seen with Heitz motor disturbances disappear almost completely after sympathectomy. From the day following the operation, when the vasodilator

[5] Leriche and Heitz: Influence de la sympathectomie périartérielle ou de la résection d'un segment artériel oblitéré sur la contraction volontaire des muscles. Société de Biologie, 17 Fevrier, 1917.

reaction was very well established, the mobility returned markedly in hands fixed immutably in position, contracted, the fingers being bent into the palms, or else turned back on the dorsal side. I am inclined to believe that a number of these severe cases are referable to disturbances of sympathetic origin, caused by the imprisonment of the nerve ends in a hard and compressing cicatrix.

(d) *The rôle of the sympathetic in the production of certain griffes cubitales.* After brachial sympathectomy I have seen a loosening up of a very rigid *griffe cubitale* which had resisted resection and suture of the nerve divided in the forearm.

I have made this observation only once, but the phenomenon was perfectly definite. It seems to me that the observation should be recorded because of its therapeutic interest.

(e) *The rôle of the sympathetic in the explanation of those motor paralyses, more or less complete, which follow certain arterial lesions,* when the nerves have not been disturbed. We call it ischemic paralysis, giving to this appellation an entirely different sense from that which we have in mind for the isolated contracture of the flexors of Volkmann. In the cases described by MM. Déjerine and Tinel there is rather complete motor paralysis with the reaction of degeneration, yet the nerves were not divided. The paralysis coincides with an œdematous infiltration of the hand with marked vasomotor disturbances which lead to true fibrous transformation of the hand. At the end of some weeks the œdema begins to diminish, the tendons and the aponeuroses are ensheathed in a veritable fibrous envelope; the muscles, already hard and tense, retract and take on a ligneous consistency. In this picture is seen the mark of the sympathetic; and in doing sympathectomy in these cases M. Heitz and I have seen vasomotor disturbances disappear, trophic disturbances improve, the tendons and the muscles become on palpation sensibly more supple, and the muscles execute slight movements. In one case, although before operation there had been complete degenerative reaction, four months after operation we observed a very definite amelioration of the electric reactions, and we are hoping for a marked functional recuperation.

I do not wish to say that sympathectomy cures the patients; and it is impossible that it should cure them at once when one considers their wounds. Unhappily, there is no cure, but to me it appears to have caused the disappearance (at least momentarily) of the stiffness of the muscles and tendons; it has assured a manifest suppling up of muscles which, after the sympathectomy, executed movements equivalent to one half the normal. Referring to the fact mentioned above à propos of *griffe cubitale*, I have the impression that the sympathetic has an enormous influence on the evolution and production of fibrous tissue. The sclerous evolution is modified, it appears, when a vasodilator reaction is brought about. Whence the conclusion that the sympathetic plays probably a large rôle in the mechanism of the so-called ischemic paralyses where the predominating feature has not the mark of ischemia. I do not mean to say that the circulatory suppression caused by the arterial lesion does not play any part, that would be absurd; what I would say is that something more is involved. But these cases are too rare in general surgical practice for me to follow the analysis alone.

(f) *The rôle of the sympathetic in the production of heel sloughs in the course of medullary lesions.* In one patient who had had flabby incomplete paralysis of the lower limbs with absence of reflexes, and incontinence of urine, there were two sloughs, one on the heel, the other on the little toe. They resisted all treatment. Three months after the wound had been received, a femoral sympathectomy was done. Three days later the ulceration of the toe was dry and cicatrized; that of the heel, which was as large as a small palm of the hand, diminished in size and was covered with active granulations. In thirty-five days it was completely cicatrized.

3. *From the Therapeutic Point of View.*—I have tried sympathectomy in a great variety of cases, and it is rather difficult for me to analyse the results, because there were often complex situations to be dealt with. Schematically, I have tried to influence the element of pain, the element of reflex contraction with vasomotor disturbances, and the trophic element. In all the cases I have had failures and disappointments.

I have done sympathectomy eleven times for phenomena of pain; once the vasodilator reaction failed. This operation was badly done and I eliminate it. For the ten others, six times there were true causalgias, and three times phenomena of pain more or less intense.

For *causalgia* I operated four times on the upper extremity, twice on the lower limb. The four cases in the upper extremity resulted as follows: One complete failure (patient operated on in the service of M. Gosset), two excellent results (complete suppression of the pains, total transformation of the patients) with final cure, now dating back 19 and 16 months. These two patients have been discharged, and are earning their living exclusively by their own work.

In a fourth case, which was very serious, I had found the brachial artery obliterated. I had not at the time thought that there would be any advantage in resecting the obliterated segment. I performed then a sympathectomy by denudation. The patient was much improved; he who for months had been confined to his bed with a wet cloth on his hand, apprehensive, indifferent to everything except his pain, got up and submitted to the same régime as his comrades; but some pains persisted. In order to improve these I again took the patient under my care and resected the obliterated arterial segment, whereupon the persisting disturbances almost completely vanished; this result promises to be permanent.[6]

In the lower limb I did one femoral sympathectomy, with appreciable amelioration. At a second operation I resected the sciatic artery and the artery of the sciatic nerve, with manifest result, but the cure has not been complete. The patient, who has been followed for six months, is entirely relieved at certain times, but has suffered much at others in damp weather. His general condition is transformed. For those who know the lamentable condition of degeneration of these patients caused by their martyrdom of pain, the words "great amelioration" have a real significance. This expression should not be taken as a euphemism masking a failure.

In another case I did a common iliac sympathectomy, which resulted in great improvement [grande amélioration] with complete transformation of the general condition. The patient has suffered at certain times, but his days of respite have been greater in number than his days of pain. This is also, to my thinking, a success worth trying for.

For all "causalgiques" the question is complex in other ways: these patients have a psychology of their own; it is necessary to isolate them somewhat and to exercise over them a little authority if we desire to cure them. Besides, they are extremely sensitive to atmospheric changes, and it seems as if their whole vasomotor system were out of equilibrium. One local operation could not pretend to set all this right at once, and these patients should not be regarded exactly as others.

I have operated *four times for phenomena of pain accompanying nerve lesions* or arterial obliterations. I had three excellent results and one complete failure.

To sum up, in the treatment of the phenomena of pain, sympathectomy cures entirely certain patients, acts very favorably in the majority of cases, but does not succeed always or always give an absolutely perfect result.

[6] In one of the last Bulletins of the Société de Chirurgie a very interesting observation by M. Le Jemtel is reported, which shows well the rôle of the sympathetic in the paretic syndrome following an obliteration of the brachial.

Five sympathectomies for *trophic ulcerations*, with or without phlyctenæ in the neighborhood, gave success five times.

I have operated three times for large *bluish œdemas* of the limbs, with one complete success; one great improvement, followed at the end of several months by complete cure; one incomplete result with partial return (in the lower limb), but on the whole, amelioration.

For reflex disturbances, eighteen sympathectomies among the patients examined heretofore (except two) either by M. Babinski, or by his assistants M. Froment and M. Heitz, and all followed up by M. Heitz, have resulted as follows:[7]

Three cures, practically complete, traced for several months, with disappearance of the vasomotor disturbances and of the contraction;

Ten ameliorations more or less considerable, some of which were almost cures;

Two ameliorations followed by incomplete return in patients who had not received any post-operative treatment. In the two cases the lasting benefit has been real;

One case in which the operation, after failure of all other treatments, has been followed by the execution of voluntary movements; also, thanks to treatment followed regularly under the direction of M. Heitz, motility is returning little by little;

Two complete failures. In these two patients there had been after operation a beginning return of voluntary motility, but the therapeutic result has been practically nil.

In all the patients who have been really benefited by the operation (16) the vasodilator reaction has been followed by a diminution of the contraction and by a reappearance more or less complete of the voluntary movements. In some cases the result has been surprising: from the day following operation the patients were able to make movements which had been impossible for months. But at the end of two or three weeks, as the vasodilator reaction subsided, the contraction shows signs of beginning anew and the movements diminish in amplitude. Observing this, we thought, with M. Heitz, that the maintenance of heat in the member operated upon was indicated. For this purpose M. Heitz has made my patients take, baths of paraffine at 60° for about one half hour. By associating with this treatment massage and reeducation Heitz has obtained very interesting results, which permit us to speak, in certain cases, of true cure.

[7] The observations will be published *in extenso* in the August number of Lyon chirurgical, under the following title: Résultats de la sympathectomie péri-artérielle dans le traitement des troubles nerveux post-traumatiques d'ordre réflexe.

Briefly then, *in the grave forms of the syndrome of Babinski-Froment* sympathectomy by itself does not suffice. But without it, the treatment usually applied soon ceases to influence the condition, and the result becomes stabilized; the operation, like so many other operations upon the nervous system, leaves room for and facilitates reeducation, and gives to it its efficacy. It is only one phase of the treatment, but it is a very rewarding phase. I insist on this point so that we shall not expose ourselves to failures all the more bitter when the operation at the outset promised to yield a brilliant result. And I recall what Heitz has recently written: [8] it is the mixed method (operation on the sympathetic followed by the treatment indicated above) which has given in the service of M. Babinski the best results.

For the paralyses connected with vascular obliterations, associated or not with nerve lesions, sympathectomies have improved the condition without giving, except in one case, a true functional result. In such case the sympathectomy should be done to modify the vascularization of the paralyzed segment, to check the fibrous regression of the muscles. It cannot constitute of itself a sufficient treatment, but it has appeared to me to be interesting and useful. The future will determine its indication.

It is the same in regard to the value of sympathectomy associated with operations upon the nerves in cases of rebellious contracture of the median or of the ulnar nerve variety. One cannot say definitely, but the question appears to me to merit consideration.[9]

In order to estimate the results of sympathectomy I have striven to be as concrete as possible: I have appraised as nil any result which was without value for the patient. The verdict may perhaps appear to be very reserved. Truly, I believe that the operation is a very interesting one and a useful expedient to which one may resort in cases, very diverse, which have been irresponsive to all other treatments; but it remains for us to define clearly the indications for it.

[8] Heitz: Des troubles circulatoires qui accompagnent les paralysies ou les contractures post-traumatiques d'ordre reflexe. Archives des maladies du coeur, Avril 1917, p. 160.

[9] Recently I tried to arrest, by sympathectomy, the appearance of gangrene after resection of the popliteal vessels. The operation was followed by complete disappearance of the pains; it changed the hue of the violet-colored spots which covered the limb. For 36 hours I hoped for a therapeutic result, but none appeared, and I had to amputate the thigh.

PUBLICATIONS

The following nine monographs:

Benzol as a Leucotoxin. By Laurence Selling, M. D. 60 pages. Price, $1.00.

Primary Carcinoma of the Liver. By M. C. Winternitz, M. D. 42 pages. Price 75 cents.

The Statistical Experience Data of The Johns Hopkins Hospital, Baltimore, Md., 1892-1911. By Frederick L. Hoffman, LL.D., F.S.S. 161 pages. Price, $2.00.

Venous Thrombosis During Myocardial Insufficiency. By Frank J. Sladen, M. D., and Milton C. Winternitz, M. D. Price, 75 cents.

The Origin and Development of the Lymphatic System. By Florence R. Sabin. 94 pages. Price, $2.00.

Leukaemia of the Fowl: Spontaneous and Experimental. By Harry C. Schmeisser, M. D. Price, $2.00.

The Structure of the Normal Fibers of Purkinje in the Adult Human Heart and Their Pathological Alteration in Syphilitic Myocarditis. By O. Van Der Stricht and T. Wingate Todd. Price, $2.00.

The Operative Story of Goitre. The Author's Operation. By William S. Halsted, M. D. Price, $3.50.

Study of Arterio-Venous Fistula with an Analysis of 447 Cases. By Curle L. Callander, M. D. Price $2.50.

are now on sale by The Johns Hopkins Press, Baltimore. Other monographs will appear from time to time

BACILLARY DYSENTERY IN CHILDREN

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SUMMARY

Introduction.
Source of Material.
Clinical Data.
Etiology (Bacteriological and Serological Data).
Dysentery Cases.
Control Series (63 cases of simple non-infectious diarrhœa and 100 normal children).
Epidemiology and Prevention.
Conclusions.
Appendix (Bacteriological and Serological Technique).

INTRODUCTION

Bacillary dysentery is a disease chiefly affecting babes and soldiers.* In the former it sometimes masquerades under the names of summer diarrhœa, infectious diarrhœa, colitis or ileocolitis, which do not have the prestige and importance that is attached to the more ominous title "dysentery." That this disease in children is caused by *B. dysenteriæ* has long been known,[1, 2, 3, 4, 5, 22] and is adequately confirmed by the bacteriological findings in our series of cases. The name "summer diarrhœa" is particularly misleading. One might as well discuss "winter cough" as was done in 1872[4] and neglect to differentiate primary and secondary pneumonia from bronchitis. There are many types of intestinal disease that occur during the warm months and there is no reason for classing them all together, for dysentery stands out sharply on clinical as well as bacteriological grounds.

SOURCE OF THE MATERIAL

The material for this report consisted of the study of 134 cases of diarrhœa. Eighty of these were in the wards of this hospital from March, 1919, to February, 1920, nine cases in the Thomas Wilson Sanitarium, Mt. Wilson, Maryland, during June and July, 1919, and 45 cases in the private practices of several physicians in Birmingham, Alabama, from July 14 to August 9, 1919.†

* The results of an investigation of an epidemic of bacillary dysentery in our troops in France (A. E. F.) will appear in a later article.

† These latter cases were studied by Dr. Harold L. Higgins and myself at the request of Dr. John Howland and with a grant of money from the Therapeutic Research Committee of the Council on Pharmacy and Chemistry of the American Medical Association. Through the courtesy of Dr. J. D. Dowling, Health Officer of Birmingham, Alabama, and Dr. J. R. Bean, we were given all the facilities in the Board of Health Laboratory. Through the efforts of Drs. Thomas D. Parke, Russell Callen, Courtney W. Shropshire and 15 other physicians, we were able to obtain stool specimens from several cases of diarrhœa in infants in Birmingham and its environs. Our sincere thanks are due these physicians and also Drs. Catherine Creighton, Harold L. Higgins, L. V. Rosenthal and C. E. Wagner for assistance with the bacteriological work.

CLINICAL DATA

Among the total 134 cases of diarrhœa, 71 were diagnosed by the clinicians as cases of dysentery (ileocolitis).

Clinically, the disease is a definite type, occurring usually in well-nourished and previously healthy children whose ages ranged from 3 months to 11 years (see Table I). The

TABLE I.—AGES OF BALTIMORE AND BIRMINGHAM DYSENTERY CASES

	Ages of all Baltimore dysentery cases	Ages of all Birmingham cases	Ages of fatal Baltimore cases	Ages of fatal Birmingham cases
Average	16 months.	25½ months.	11 months.	15 months.
Mean (excluding wide extremes)	14 months.	17 months.	5½ months.	12 months.
Minimum	3 months.	6 months.	4 months.	6 months.
Maximum	36 months.	132 months (11 years).	36 months.	30 months.

ages of the Birmingham patients were higher than those of Baltimore. This may possibly be explained by the fact that in the former breast feeding was a more general rule and therefore the younger children escaped infection.

With one or two doubtful exceptions, none of the patients was exclusively breast fed, but received supplementary feedings of whole milk, proprietary foods or general diet.

The onset was usually characteristic and sudden (see Table II). The child lost his appetite and showed evidence

TABLE II.—CHARACTER OF ONSET OF BALTIMORE DYSENTERY CASES *

	Sudden onset with fever	Insidious onset	Dysenteric infection occurring during course of other disease	Vomiting at onset	Irritability and nervous symptoms at onset	Convulsions at onset	Loss of appetite and refusal of food at onset	Previous intestinal disease (several months prior to dysenteric infection)	Average time of appearance of blood in stool after onset
No. of cases	23	4	2 cases, (1 osteomyelitis, 1 scurvy).	14	14	6	10	3	2.3 days.
Percentage	79	14	7	52	48	21	34	10	

* Analysis based on 29 cases in which the histories were complete.

of having fever. Irritability, vomiting and convulsions were frequent initial symptoms. Within a few hours there was an increase in the number of stools. These were at first fecal, rarely green, becoming blood-tinged on the second day, and within four days consisted almost entirely of blood and mucus. The number of stools ranged from 3 to 30 a day. The size of the stool was usually small and seemingly out of proportion to the patient's straining efforts.

The fever subsided in most cases by the fifth day. The patients were usually quite ill, crying feebly when disturbed, were drowsy and apathetic, after their initial irritability had ceased, and had little or no appetite. Loss of sleep due to the frequent and often painful bowel movements was a distressing factor. Dehydration and marked loss of weight was evident by the end of the first week.

In the patients that recovered, the blood disappeared from the stools during the second week and the diarrhœa abated by the 14th day.

Such was the course in 79 per cent of our cases. In 14 per cent (4 cases), however, the picture was misleading. With these four children, there was no sudden onset. They had been under observation for over one month with symptoms of intestinal indigestion; *i. e.,* occasional vomiting and from three to six loose green stools a day which frequently contained mucus. Their weight was stationary or showed slight losses and they were malnourished. After several weeks of these symptoms, the stools became blood-tinged and were increased in frequency to nine or eleven a day. The temperature was slightly increased. This picture remained unchanged for several days and then the condition returned to the former state of mild diarrhœa. During the period of bloody diarrhœa *B. dysenteriæ* (Flexner) was isolated from the stools of three of these four cases and agglutinins for *B. shigæ* were demonstrated in the serum of the fourth. Were these four cases instances of chronic dysentery that had become worse or did the bloody diarrhœa represent a dysenteric infection that had become superimposed on a previously inflamed intestinal mucosa? The latter appears to be the more probable explanation.[7]

Such cases must be distinguished from cases of intestinal indigestion in which the stools contain streaks of blood (usually bright blood) for only one or two movements and never longer than one day. This blood is probably the result of mechanical irritation of the lower rectum due to straining. The cultural results in such cases were negative.

In two other patients there were histories of intestinal indigestion several months previously, from which they had completely recovered. There were no agglutinins for *B. dysenteriæ* in the serum of the only one that was tested during this earlier period; yet when he came into the hospital four months later with clinical dysentery, the reaction was positive, so that it would seem probable that the previous diarrhœa had no connection with the later dysenteric infection.

However, it must not be forgotten that in adults a mild non-bloody diarrhœa lasting only 24 hours has been proven to be due to dysenteric infection.[8] There is no reason to suppose that similar cases cannot arise in children.

In two other cases (seven per cent) the diagnosis of dysentery was marked by the presence of other diseases; in one by scurvy (proven by X-ray) and the other by osteomyelitis. *B. dysenteriæ* (Flexner) was isolated from the stools of each of these cases.

In the dysentery cases in Baltimore and Birmingham there were 67 white children with 14 deaths and 4 colored with 1 death, a total mortality of 21 per cent.*

An analysis of the ages of the fatal cases in Table I would seem to indicate that the younger patients were more vulnerable.

The leucocyte count of the Baltimore cases was slightly increased.[9] The mean was 13,000 for all cases and 13,700 for those that died. Wide variations, without obvious cause such as otitis media, were, however, to be noted. In fact the leucocyte count was of little or no diagnostic importance.[10]

The physical findings were of little assistance. In only one case was the spleen palpable. The liver was occasionally somewhat enlarged and tender. Abdominal tenderness was not marked. Five of the patients were emaciated on admission and two had obvious rickets.

Complications were infrequent.[11] Pyelitis occurred in one case, *B. coli communis* being isolated from the catheterized urine. Otitis media developed in two cases. Hyperpnœa[12] occurred in three cases.

It is frequently stated that after recovery from dysentery (ileocolitis) the feeding of the small patients may become a difficult problem. This has occurred in very few of our cases. Occasionally there was persistent refusal to take food so that gavage was necessary for a few days. With these exceptions, all of the other patients took their feedings well and showed a steady increase in weight; after three months they were well-nourished, exceedingly healthy children. No case became chronic.

Clinically (as well as bacteriologically) there was no difference between the cases we saw in Birmingham and those that we have studied in Baltimore. However, the ratio of dysentery (ileocolitis) cases to those of simple non-infectious diarrhœa was 8 to 1 in Birmingham and 1 to 2 in Baltimore.

The post-mortem diagnoses in practically all of the children that died of uncomplicated dysentery were definite diptheritic or ulcerative or acute necrotizing enterocolitis depending on the nomenclature of each pathologist. In fatal cases in children suffering from malnutrition, scurvy, rickets or other diseases in which dysentery had acted as the last straw, as a complicating and not the primary cause of death, the post-mortem diagnoses of the intestines ranged from normal to hyperemia or slight ulceration of the lymph follicles of the lower third of the ileum and the colon. In other words, the autopsy revealed the severity of the infection and the virulence of the causative organism. It is frequently stated that the degree of ulceration of the intestine depends upon the length of the illness. This statement did not appear to be true in this series of cases.

The autopsy of one case of Flexner dysentery of but three days' duration showed the ulcers and membrane formation of typical acute enterocolitis.

*** The mortality for these 1919 cases was lower than that of former years, for among 114 cases treated at the Harriet Lane Home from 1912 to 1918 inclusive, there were 33 deaths, a mortality of 29 per cent.**

Three days after the death of this patient, his brother developed clinical dysentery which cleared up after an illness of two weeks. *B. dysenteriæ* (Flexner) was isolated in this case also.

Similar findings occurred in the remaining uncomplicated fatal dysentery cases. Occasionally in addition to the ulceration of the lower third of the ileum and the colon, there were evidences of fatty degeneration of the liver. These probably correspond to the findings reported by Parke in cases in Birmingham.[33]

ETIOLOGY—BACTERIOLOGICAL AND SEROLOGICAL DATA

DYSENTERY CASES

In Birmingham, Alabama, from July 14 to August 9, 1919, I cultured one or more specimens of the stools of 40 patients with clinical dysentery. Only half of these were in the acute stage of the disease and from only 13 did we obtain satisfactory specimens because all of the patients except two were in private homes scattered throughout the city and it was often impossible for us to be notified until the stool specimen had become too old to give reliable bacteriological results.

Of the 13 cases from which we received satisfactory stool specimens, I recovered *B. dysenteriæ* (Flexner) * in six cases, *B. dysenteriæ* (Shiga) in one and *B. dysenteriæ* (Kruse *E*)[14, 15] (or *B. dispar*)[16] in one. (A description of the technique employed is appended.) Positive agglutinins for *B. dysenteriæ* (Shiga) were demonstrated in the sera of two additional patients. (The latter were brother and sister in a family in which one child had died the week previously of clinical dysentery and both parents were convalescent from dysentery.) In other words, in these thirteen cases, infection with *B. dysenteriæ* was demonstrated in ten.

Of the 31 cases of clinical dysentery in the wards of this hospital, *B. dysenteriæ* (Flexner) was recovered in eighteen. Positive agglutinins for *B. dysenteriæ* (Flexner) were demonstrated in seven additional cases and for *B. dysenteriæ* (Shiga) in one further case. Three were negative culturally but agglutination reactions were not done and two were negative bacteriologically and serologically. In other words, infection with *B. dysenteriæ* was shown in over 83 per cent of the cases of clinical dysentery in the Harriet Lane Home during the past year.

The ratio of Flexner to Shiga infections was 8 to 1. The Flexner bacillus is usually the more common type in children.[2, 53, 54, 55] In fact, some investigators [53, 56] found mixed infections with both varieties more frequently than the Shiga type alone.

The dysentery agglutination reaction assists the diagnosis of dysentery.[2, 4] It is essential, however, for each worker to standardize his cultures and technique with normal control sera, especially in Flexner infections, inasmuch as the agglutinability of different strains of this organism varies considerably. Freshly isolated strains should not be used, for their agglutinability is inconstant. I have used the standard agglutinable cultures issued by the Department of Pathology, University of Oxford, on behalf of the Medical Research Committee (England) and also formalized cultures made according to Prof. Georges Dreyer's [17] instructions and found (Table III), as he states, that macroscopic dysentery agglutination by a patient's serum with standard agglutinable cultures or comparable preparations in a dilution 1:30 (6-8 units) is suggestive and a titre of 1:50 (10 or more units) is diagnostic of previous or present dysentery infection.*

TABLE III

Case no.	Age at onset	Agglutination reactions of the patient's serum			Type of dysentery bacillus isolated from stool culture
		Days after onset	Flexner culture	Shiga culture	
23	7 months.	2	? 1/25	0 1/25	
		4	± 1/25	0 1/25	
		9	+ 1/50	0 1/20	
82	5 months.	6	± 1/200	+ 1/50	
58	4 months.	6	0 1/20	0 1/20	Flexner (inagglutinable).
11	24 months.	7	+ 1/500	0 1/29	Flexner.
10	15 months.	9	+ 1/200	Not done.	Flexner.
16	36 months.	9	+ 1/100	0 1/20	
		15	+ 1/250	+ 1/50	
78	11 months.	13	+ 1/20	Not done.	Flexner.
54	30 months.	14	+ 1/100	0 1/29	Flexner.
79	9½ months.	17	+ 1/200	0 1/20	Flexner.
		21	+ 1/100	0 1/20	
80	26½ months.	19	+ 1/200	0 1/20	Flexner (urine culture).
		38	+ 1/200	0 1/20	
46	36 months.	21	+ 1/1000	0 1/20	Flexner.
8	19 months.	134 before onset.	0 1/25	0 1/25	
		21 after onset.	+ 1/50	0 1/20	
		158 after onset.	+ 1/20	0 1/20	
77	8 months.	26	± 1/50	0 1/20	Flexner.
		76	+ 1/50	0 1/20	
42	22 months.	27	+ 1/100	0 1/20	
44	23 months.	37	± 1/20	0 1/20	
50	3½ months.	38	0 1/20	0 1/20	
		140	0 1/20	0 1/20	
59	14½ months.	39	+ 1/100	0 1/20	
		138	± 1/50	0 1/20	
63	6½ months.	68	+ 1/20	0 1/20	Flexner.
		172	0 1/20	0 1/20	
56	3 months.	90	+ 1/20	0 1/20	Flexner.
45	17 months.	176	0 1/20	0 1/20	Flexner.
41	14 months.	184	± 1/20	0 1/20	Flexner.
39	23½ months.	200	± 1/50	0 1/20	Flexner.
40	11 months.	205	± 1/200	0 1/20	Flexner.
2	48 months (4 years).	18	0 1/25	± 1/50	
4	132 months (11 years).	20	0 1/25	+ 1/125	
37	14½ months.	45	0 1/20	+ 1/50	

Five Flexner antigens (cultures) English (Murray) types V, W, X, Y and Z were used for agglutination, and the reactions denote the highest titres for any one of them. All of these patients had clinical dysentery.

* By *B. dysenteriæ* (Flexner) I refer to the whole group of mannite fermenting dysentery bacilli.

* In infants and young children a positive dysentery agglutination even at a dilution of 1:20 early in the disease is very suggestive. In my experience non-specific agglutination in young children is infrequent.

In all patients from whom an agglutinable *B. dysenteriæ* was recovered and whose sera were tested, specific agglutinins were found. In only three patients who were not, at that time, suffering from bloody diarrhœa did I demonstrate dysentery agglutinins (*vide infra*).

The literature on this subject is contradictory. It is frequently stated that the patient's serum reactions in dysentery are worthless.[33] It is just as frequently claimed that they are infallible. Glynn and his co-workers[29] give an excellent analysis of the various methods and insist that agglutination, if done with standardized methods, is reliable.

The confusion on this question is readily explained. If a freshly isolated living culture of *B. dysenteriæ* is used for agglutination, a positive result may be obtained with a known serum in a dilution of 1:500. A few weeks later the same serum and a subculture of the same *B. dysenteriæ* strain may give a positive agglutination at an end titre of only 1:100. In other instances a freshly isolated *B. dysenteriæ* culture may be agglutinated only at the end titre of 1:100. Yet after a few weeks of laboratory cultivation, positive agglutination may be noted with the same serum at a titre of 1:500.

Obviously, then, if a laboratory worker tests the sera of normal persons with either of these two types of culture, his figures are useless for later comparison with the agglutination results of patients with dysentery.

If living cultures of older laboratory strains are used, this difficulty may be remedied though not cured, for although strains that have been artificially cultivated for long periods have reached quite a constant level of agglutination, yet there is still some variation. Furthermore, the emulsions of these living cultures will vary in opacity and thickness from day to day. This will also give confusing results for agglutinations with the same serum, and emulsions of the same strain which are of different opacity will give different end titres. Thinner emulsions, within certain limts, will be agglutinated by the same serum in higher dilutions than those that are more opaque.[30]

These are some of the arguments Dreyer, Ainley, Walker, Gibson and others[31, 37, 38] have advanced in support of the Oxford Standard agglutinable cultures. It is not to be denied that conflicting results have been obtained by some investigators[39] with Dreyer's method. In the main, however, they have been most satisfactory and results in different laboratories are thus comparable.

Furthermore, it is not as clearly recognized as it should be that while there is but one type of Shiga dysentery bacillus, there are at least five subdivisions of the mannite-fermenting group. Murray[35] has designated these as *B. dysenteriæ* (Flexner) types V, W, X, Y and Z (based on agglutination) and has dropped the older subgroup names of Flexner, Harris, Hiss-Russel-Y and Strong (based on the differences in fermentation of maltose and saccharose). If agglutination reactions with patients' sera are done with only one or two types of the Flexner bacillus as antigens, obviously some positive tests may be missed.[36]

I have studied 89 cultures * of mannite-fermenting dysentery bacilli isolated from these cases and was able to differentiate them culturally into seven divisions on the basis of the fermentation of maltose, saccharose, dulcite and rhamnose. These cultures were also differentiated serologically by their agglutination reactions with Murray's five (English) Flexner monovalent rabbit sera, types V, W, X, Y and Z. These serological divisions did not run parallel with the fermentative divisions. A general correspondence existed between the serological types of the organisms isolated from the patient's stool and agglutination reactions of his serum. One or the other and not both of these methods of division must be adopted. The classification by agglutination is advisable, because it is simpler and more rapid. The results of the agglutination reactions of the patient's serum may be expressed in the same terms as the serological typing of the organisms from his stool. Fermentation is less constant and gives rise to more divisions than there are carbohydrates.

The serological reactions of these type sera, as Murray states, show cross-agglutination to a greater or less extent but they indicate that there are five antigens V, W, X, Y, Z and probably others, one or more of which predominates in a given strain. Polyvalent diagnostic and therapeutic dysentery sera are practically worthless unless they include antibodies for the more common of these types.

In the agglutination reactions recorded in this paper, eight dysentery antigens were used, *i. e.*, Shiga, Flexner types V, W, X, Y and Z, *B. dispar* (or Kruse E) (a lactose fermenting dysentery) and B. ambiguus, Schmidtz[40] (an indol producer which forms acid and no gas in dextrose and rhamnose).

As will be seen in Table III, suggestive agglutination was noted in one case (No. 23) on the second day,[34] the titre rising on the fourth and ninth days. The maximum is probably on the 17th to 21st day as it is in typhoid. From the stool of one patient (No. 58) a dysentery (Flexner) bacillus, that did not agglutinate with any of the five diagnostic type sera, was isolated and this patient's blood serum had no agglutinins for the V, W, X, Y and Z stock cultures, suggesting that there are additional types in the Flexner group.[36] Agglutinins for both Shiga and Flexner groups were noted in only two cases.[34, 36, 37]

Agglutinins persisted in several cases longer than four months and in three cases tested after six months they were still present.[34]

CONTROL SERIES (63 CASES OF SIMPLE DIARRHŒA † AND 100 NORMAL CHILDREN)

In addition to the 71 cases of clinical dysentery just described there were 63 patients studied who developed increased frequency of stools at one time or another during the course of other illnesses. The clinical diagnoses of these latter were

* A paper on the "Divisions of the So-Called Flexner Group of Dysentery Bacilli" will appear later.

† The term simple or non-infectious diarrhœa or merely diarrhœa is used in contradistinction to the bloody diarrhœa of dysentery.

gastro-intestinal indigestion (47,) typhoid fever (6), pyelitis (3), tuberculosis (2), hydrocephalus (1), eczema (1), bronchopneumonia (1), scurvy (1) and endocarditis (1).

The onset of the increased frequency of stools in each of these cases was insidious. There was no irritability or increased temperature. Several of the patients vomited occasionally, but loss of appetite was not obvious. Practically all gave histories of diet indiscretions especially of high sugar feeding. The stools were always fecal, usually green and contained no blood. Only in cases of long duration was mucus present in excess. In fact, in none of this group with the exception of the typhoid cases was there evidence of an acute intestinal infection.

The study of the stools of these 63 cases of simple † or non-infectious diarrhœa, as well as those of 100 normal children, serves as an admirable control series for the studies on the cases of dysentery, for in none of the former (63 cases of diarrhœa and 100 normal children) did we obtain *B. dysenteriæ* from the stools. The sera of three patients among sixteen with diarrhœa tested showed positive dysentery agglutinations. Two of these gave histories of bloody diarrhœa some months before admission and, as shown in Table III, agglutinins may persist in the blood six months after a dysenteric infection. The third had typhoid fever and there is evidence to show that one infectious disease may raise the non-specific agglutinin titre.[27]

The negative cultural results in these cases of simple diarrhœa and in normal children when contrasted with the positive findings in 83 per cent of the cases of bloody diarrhœa indicate plainly that children presenting a symptom-complex as outlined in Table II are suffering from bacillary dysentery.

Indeed it would seem that a correct differentiation of dysentery from diarrhœa can be made in most instances on clinical data alone.

The bacteriological and serological results indicate that the Birmingham and Baltimore cases were of a similar type.

The results in Baltimore and Birmingham bear out the conclusions of Tenbroek and Norbury in Boston in 1914 and 1915[5] that ileocolitis in children is due to infection with dysentery bacilli. Duval and Bassett[1] in 1902 and the Rockefeller Commission in 1903[2] demonstrated *B. dysenteriæ* in a high percentage of cases that they called "summer diarrhœa," but a clinical analysis of their cases shows that it was usually from the bloody and mucous stools of patients with typical dysentery that these organisms were isolated.

In fact, it would seem that ileocolitis and bacillary dysentery in children in Boston, Baltimore, Birmingham, New York and probably other cities are one and the same disease.

Some investigators have given significance to the presence of *B. welchii* (gas bacillus) in the stools of patients with diarrhœa.[29] They have also gone further and outlined special treatment and diets for this so-called "gas bacillus diarrhœa." However, this was soon contradicted, but although Simonds,[29] Knox and Ford[30] and others[5, 31] have conclusively proven that *B. welchii* is an inhabitant of the intestines of normal children, some pediatrists are still influenced by its presence. I have often found *B. welchii* in normal stools and am convinced that it plays no part in the etiology of clinical dysentery or non-infectious diarrhœa. Those who have studied war wounds realize that *B. welchii* does not produce dire results except in tissues where its supply of oxygen is limited. How can it be pathogenic in intestinal contents which are freely moving and well supplied with oxygen?

Perhaps the clearest analogy is found in tetanus. *B. tetani* is pathogenic in deep wounds yet it is common knowledge that this organism is frequently found in horse feces. Has any one accused the horse of "tetanus diarrhœa"?

B. Morgan No. 1 has been asserted to be the cause of diarrhœa in children, especially in England.[32, 33] In this series of cases I have found this organism frequently associated in the same stools with *B. dysenteriæ*. I have found it in many cases of simple diarrhœa in children and also in many adults. In no case, in which serological tests were made, did the patient's serum agglutinate *B. Morgan No. 1*. Tenbroek and Norbury[5] and Thjotta[34] report similar results. As a matter of fact the British investigators found Morgan bacilli in the stools of many normal children. In very few of their diarrhœa cases were the stools bloody and it is open to doubt whether they were dealing with cases similar to our clinical dysentery. Lewis[35] and Kligler[36] have shown that *B. Morgan No. 1* probably represents a wide group of organisms rather than a single type. I have carried out agglutination tests with four of Kligler's diagnostic rabbit sera and 50 strains of Morgan No. 1 isolated from diarrhœal and normal stools and found that there is no uniformity in results and that many strains are inagglutinable, while others are agglutinated by more than one serum.

It is generally agreed that in specific intestinal infections such as typhoid, paratyphoid and bacillary dysentery the causative organisms produce agglutinins in the patient's serum. Furthermore, *B. typhosus, B. paratyphosus* and *B. dysenteriæ* are not found in the stools of normal cases except in occasional carriers who practically always give a history of having had typhoid or dysentery. *B. Morgan No. 1* does not fulfill either of these postulates so that it would seem improbable that this organism could be the specific cause of an intestinal infection like dysentery.

B. pyocyaneus,[37] *Streptococcus fecalis*[38, 39] and *B. proteus*[5, 38, 40] can be similarly discounted as etiological agents in diarrhœa, for they are to be found in the stools of many normal children.

The theory[41, 21] advanced during the last century by French and German writers that infantile diarrhœa was caused by highly virulent colon bacilli has died a natural death from lack of confirmation.

EPIDEMIOLOGY AND PREVENTION

Our studies in Birmingham revealed in many cases a well-defined history of contact infection from a neighbor's child or from an adult with a mild diarrhœa; in several instances in Baltimore two cases occurred in the same house.

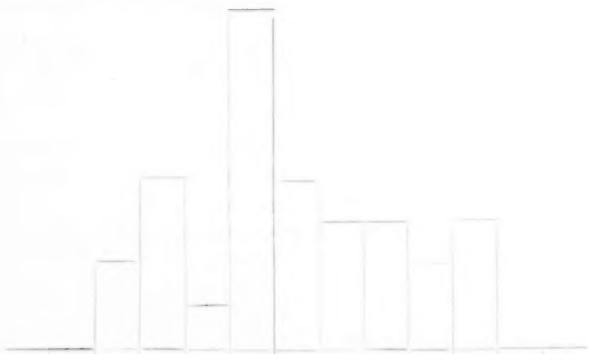
An examination of the source of the milk supply showed that the dairy could not be the origin of the infection. Studies in adult dysentery have shown that although wide-spread epidemics may occasionally be water-borne, dysentery bacilli are rarely recovered from central milk or water supplies.[24, 42, 34] It is sometimes maintained that inasmuch as the majority of the children suffering from dysentery are of the crawling age, the disease may be acquired through the child's fingers becoming soiled from the floor. It would appear in our series that the infection of the milk in the individual household by flies or the mother's fingers is also a possible explanation of its spread.

That the boiling of milk and milk mixtures before feeding has a most important influence on the prevention of diarrhœal diseases has always been suspected and Knox and Powers [46] have found that the use of boiled milk mixtures in boiled containers has greatly reduced the incidence of dysentery among the children whose feedings have been supervised by the Babies Milk Fund Association of Baltimore.

That flies have been the means of carrying dysenteric infection has been clearly shown by the studies of Graham Smith [44] and others.[45] The epidemiology of the outbreaks of dysentery in Salonika [34] during the war has proven beyond a doubt that flies were offending agents during the summer months.

The curve (see Table IV) showing the data of onset of our cases in Baltimore demonstrates that the majority of the cases occur during the height of the fly season. Table IV also shows the fallacy of calling dysentery in children "summer diarrhœa" for although the greatest incidence was in August, yet cases occurred regularly during the winter months.

TABLE IV.—INCIDENCE OF BALTIMORE DYSENTERY CASES


Mar. 1919 0 cases.
Apr. 1919 0 cases.
May 1919 2 cases.
June 1919 4 cases.
July 1919 1 case.
Aug. 1919 8 cases.
Sept. 1919 4 cases.
Oct. 1919 3 cases.
Nov. 1919 3 cases.
Dec. 1919 2 cases.
Jan. 1920 3 cases.
Feb. 1920 0 cases.
Mar. 1920 0 cases.

Conradi in Metz [46] and Ohno in Japan [47] demonstrated *B. dysenteriæ* in mild cases and normal individuals who had been in contact with dysentery patients during the winter months, so the probabilities are, that dysentery bacilli, which live with difficulty outside of the human body, weather the winter by means of chronic or mild cases or carriers and in the spring are ready for wider dissemination by flies.

The lesson to be drawn from these epidemiological studies is obvious. Children should be breast fed or given only boiled milk in boiled containers. Children and milk should be protected from flies. When cases occur, the stools should be completely covered so that flies do not have access. Almost invariably mothers will save specimens, for the visit of the doctor, either wrapped in a newspaper or in an imperfectly covered receptacle. Those engaged in caring for a patient with dysentery should not prepare food for other children. These recommendations seem self evident but they are necessary and are difficult to enforce rigidly.

Whether inoculations with dysentery vaccines will prove of value in children is problematical. Heretofore the severe reactions to these vaccines have prevented their use except in the face of a grave epidemic,[48] but the recent work of Graeme Gibson [49] in the British Army would seem to indicate that the reactions may be eliminated without impairing the value of the protection. Wholesale inoculations will probably never be necessary but eventually it may prove of value in cities that have a high incidence of infantile dysentery.

At present the treatment of this condition, as of typhoid fever, is merely palliative and does not seriously affect the mortality, yet the stamping out of this disease by suitable quarantine by Health Departments is an attractive possibility. This can only occur by recognizing that ileocolitis is caused by dysentery bacilli and reporting it as dysentery. Just as the clinical name of enteric fever was changed to typhoid and paratyphoid fever, so ileocolitis and infectious diarrhœa should be renamed in accordance with their etiology as dysentery in children. This plea was made in 1903 by Knox [9] following Duval and Bassett's pioneer work, but the old names still persist. One great advantage to be obtained from such a change of nomenclature would be the making of the disease reportable. In many of our cities dysentery is a reportable disease but ileocolitis attracts no official notice. Inasmuch as in our series of cases, bloody stools and a febrile onset are practically pathognomonic of dysentery, it would seem that the majority of cases can be recognized on clinical grounds and reported to the health authorities.

Conclusions

1. Over 80 per cent of the acute cases of ileocolitis both in Baltimore and Birmingham were due to infection with *B. dysenteriæ*.

2. *B. dysenteriæ* (Flexner) is more prevalent than *B. dysenteriæ* (Shiga) in Baltimore, Maryland, and Birmingham, Alabama.

3. Clinically as well as bacteriologically the Baltimore and Birmingham cases were identical.

4. *B. dysenteriæ* (either Flexner or Shiga) was not found in the stools of 63 cases of simple diarrhœa nor in those of 100 normal children.

5. The name ileocolitis should be changed to dysentery in children and the disease made reportable to the health authorities.

6. Dysentery (ileocolitis) is probably spread from the stools of one patient to the food and mouths of other children by flies and infected hands and not disseminated from a general dairy source.

7. Dysentery is less prevalent among children receiving breast milk or boiled milk and boiled milk mixtures in boiled containers.

8. The agglutination reactions of the patient's serum by standardized technique is of assistance in the diagnosis of dysentery.

9. *B. Morgan No. 1, B. welchii, B. pyocyaneus, B. proteus* and the *Streptococcus fecalis* are not the cause of dysentery (ileocolitis) or diarrhœa.

APPENDIX

BACTERIOLOGICAL AND SEROLOGICAL TECHNIQUE

Stool Cultures.—A loop full of bloody mucus (unwashed) was streaked first over the surface of one Endo plate,* and then a second Endo plate without flaming the loop. After 18 hours' incubation at 37.5° C. the colorless colonies were fished into tubes of Russell's double sugar medium[20] (Andrade's[21] indicator). Those cultures that had colorless slants and red butts without gas after 18 hours' incubation were subcultured in gelatin and 7 Durham fermentation tubes of peptone water containing respectively 1 per cent of lactose, dextrose, mannite, maltose, saccharose, dulcite and rhamnose (Brom-cresol-purple indicator).[22]

The growth from the original culture (Russell's slant) was then emulsified in saline and agglutinated at 55° C. for four and one-half hours with polyvalent dysentery, Flexner and Shiga type, sera. Six- to eight-hour peptone water cultures were examined for motility and seven-day peptone water cultures were tested for indol by ether extraction and Ehrlich's reagent.†

The fermentation cultures were incubated at 37.5° C. and read at intervals, for over 21 days and the gelatin cultures were left at room temperature for 28 days.

The necessity for prolonged incubation of fermentation cultures is shown by the fact that 12 per cent of the cultures from children in this series and 29 per cent of those from the series in troops in the A. E. F. were late lactose fermenters, that is, colorless colonies on Endo's medium that fermented lactose after the second day of incubation. However, all fermentations were practically complete by the 14th day and only very slight changes occurred during the remaining time of the 21-day incubation. It would seem that 14 days' incubation for fermentation cultures is sufficient and not 21 days as often stated.

Agglutination.—Subsequent agglutination work to confirm the original tests was done with 18-hour peptone water cultures. For the diagnostic sera employed, I am indebted to the Rockefeller Institute for polyvalent dysentery, Flexner and Shiga, sera; to Dr. A. D. Gardner and the Medical Research Committee of England for typhoid, paratyphoid A and B, Shiga and Flexner V, W, X, Y and Z sera; to Captain E. G. D. Murray, R. A. M. C. for Kruse E, Schmitz, Shiga and Flexner V, W, X, Y and Z sera; and to Prof. F. W. Andrews for Z serum.

Dreyer's[23, 17, 24] technique was used to test the patient's serum for agglutinins. Inasmuch as I used eleven different antigens in this work I had to adopt the following modification of this method. The patient's serum (at least 1.0 c. c. was required) was diluted ten times. 0.5 c. c. (or 10 drops) of this diluted serum was placed in each of 11 agglutination tubes; 0.5 c. c. (or 10 drops) of a formalized standard agglutinable culture of each of the following organisms was placed in one of these 11 tubes; *B. typhosus, B. paratyphosus A, B. paratyphosus B, B. shigæ, B. dysenteriæ* (Flexner), English types V, W, X, Y and Z, *B. dysenteriæ* (Kruse E) (or *B. dispar*) and *B. dysenteriæ* (Schmitz) (or *B. ambiguus*).

These tubes were incubated in a water bath at 55° C. for four and one-half hours. (Agglutination reactions with *B. dysenteriæ* require longer incubation than those with *B. typhosus*. Four and one-half hours at 55° C. is the minimum time.) If agglutination was positive for any of these 11 cultures, tests were set up according to Dreyer's directions using only those standard agglutinable cultures for which there had been agglutinins in the preliminary test.

* Endo's medium employed was made as follows: Shred agar 20 grams; peptone (Difco) 10 grams; meat extract 5 grams; NaCl 5 grams; distilled or tap water 1000 c. c. Boil; adjust reaction to pH 7.8, filter and autoclave in 100 c. c. lots in flasks for 15 minutes at 15 lbs. Ten per cent lactose in distilled water was similarly autoclaved in 10 c. c. lots in test tubes.

To pour plates: Add 0.25 c. c. of 10 per cent basic fuchsin (in 95 per cent alcohol) to a flask of 100 c. c. of melted agar. Dissolve 0.5 gm. of sodium sulphite in a test tube of 10 c. c. of 10 per cent lactose and add the solution to the fuchsin agar. This will completely decolorize the agar. Pour into 7 100 mm. Petri dishes.

† Glynn's method.[19]

0.5 c. c. of ether was poured into the 7-day peptone water culture tube and the tube shaken. The supernatant ether was then pipetted off and stratified on 1.0 c. c. of distilled water in an agglutination tube. 0.25 c. c. of Ehrlich's reagent (paradimethylamidobenzaldehyde 4 parts; alcohol (95 per cent) 380 parts; hydrochloric acid (conc.) 80 parts) was then allowed to flow down the inside of the tube. A purple layer at the ether-water junction within 30 minutes denoted the presence of indol. This method obviates the difficulty of differentiating true indol reactions from the subsidiary colors due to the peptone culture media. *Alternatively* the Ehrlich reagent may be carefully added to the culture tube after shaking with ether so as to form a layer between the ether and the culture medium. The pseudo-indol reactions that occasionally are noted in this latter method may be distinguished by adding 0.5 c. c. of chloroform, for the true rosindol color is soluble in chloroform.

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A STUDY OF THE BEHAVIOR OF SYPHILITIC AND NORMAL SERA TOWARDS CERTAIN COLLOIDAL SOLUTIONS

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The addition of a solution of protein, under favorable conditions, to many different colloidal solutions is followed after a certain time interval, often several hours, by a definite change in the mixture. Either a visible flocculus forms, or the solution "sets," or in some instances its color changes. The last outcome is best seen when solutions of colloidal gold are employed as in the Lange gold-sol reaction of the cerebrospinal fluid.

The reaction of protein solutions with various colloids was observed in connection with the Wassermann reaction early in the development of the test although its true significance was not then recognized.

Michaelis[1] added inactivated luetic serum to a properly diluted alcoholic extract of syphilitic liver antigen and incubated the mixture at 37° C. for five hours. At the end of that time definite flocculation was present in the tube containing luetic serum, and the controls (non-luetic serum) showed no turbidity. From this isolated observation he drew the false conclusion that the Wassermann reaction was a specific precipitin reaction.

Some time later Porges and Meier,[2] working with a lecithin colloidal solution, observed the same phenomenon. A one per cent alcoholic solution of lecithin was added drop by drop to physiological salt solution, with constant shaking, until the resulting mixture contained 0.2 per cent of lecithin. To one part of this colloidal solution an equal amount of inactivated human serum was added and the mixture was incubated at 37° C. for five hours. Various syphilitic and non-syphilitic sera were tested in this way and the results controlled by complement fixation reactions. As a rule, flocculation occurred only in the tubes containing Wassermann positive sera, although the results were in many instances doubtful and in some cases false.

Recently Vernes[3] and his collaborators have studied the physical properties of luetic and non-luetic sera by the use of colloidal solutions of iron and of a cholesterinized organ extract colloid called by them "perethynol." The results of this work are of great interest and throw some new light on the complement fixation reaction in syphilis.

The important conclusions of Vernes may be briefly stated, although the original work must be consulted for details of the methods employed. These are:

1. Luetic sera differ from normal sera in their power to produce flocculation when added to colloidal solutions.

2. A few sera fall into a common zone where it is impossible to distinguish a syphilitic serum from a normal serum by flocculation reactions.

3. This zone varies with the colloidal solution employed and with the concentration of electrolytes.

4. The most accurate results were obtained by the use of sera which had been inactivated at 56° C. for 20 minutes.

These various observations show clearly that there is a physical difference between luetic and normal sera which can be demonstrated by very simple laboratory methods. Sachs and Georgi[4] have lately advocated the use of the flocculation reaction as a diagnostic test for syphilis, but the

reports[5,6] on its reliability have varied, no doubt owing to the technical difficulties encountered in determining the results. It seemed advisable, therefore, to study the phenomenon on sera controlled by the Wassermann reaction, using various colloidal solutions, electrolytes and H-ion concentrations.

METHODS AND REAGENTS

The following solutions were used in the preparation of colloidal solutions:

1. One per cent lecithin in alcohol.
2. Acetone insoluble antigen of Noguchi.
3. One per cent lecithin plus 0.2 per cent cholesterin in alcohol.
4. One per cent mastic in alcohol.
5. Various concentrations of sodium oleate in water.
6. Alcoholic beef heart extract plus 0.2 per cent cholesterin.

The colloidal solution was prepared by adding one of the above solutions drop by drop to physiological saline, with constant stirring, until the required concentration was obtained.

The sera were inactivated at 56° C. for 20 to 30 minutes, in a water-bath. Most sera were less than 24 hours old.

Various concentrations of NaCl, $(NH_4)_2SO_4$ and $CaCl_2$ were employed as electrolytes.

To carry out the reaction it is necessary to add to a series of clean, small test-tubes various amounts of colloidal solution, electrolyte and normal serum, and to a parallel series of tubes the same solutions in the same amounts, but replacing normal serum by known luetic serum. The tubes are then placed in an incubator at 37° for 15 to 20 hours, when the results are determined.

Flocculation is most easily seen by transmitted light, against a dark background, exactly as is the case when searching for a faint trace of albumin in the urine. The presence of heavy flocculation is easily determined as is the complete absence of a flocculus. If, however, there is a very fine but definite suspension of small refractile particles evenly suspended throughout the liquid, the result will depend on the size of the particles and the results of the controls. A barely visible flocculus is often present with known non-luetic sera and it is necessary to take account of this in reading the final result. A small hand-lens is of some help, but higher magnification will show that flocculation has occurred in practically every tube. Even with controls and the aid of magnification some results will be doubtful.

After numerous preliminary experiments to determine the influence of the various proportions of reagents and the effect of electrolytes, etc., the following conclusions were reached:

1. Inactivation of complement by heating the serum at 56° for 20 minutes is necessary to reduce the number of doubtful and falsely positive results.

2. A minimum amount of electrolyte is probably necessary, but this need not be over 1 per cent NaCl in the mixture. Eight per cent NaCl solution was used, but results were equally as good with 6 per cent and 10 per cent solutions.

3. H-ion concentration has no noticeable influence within the range of phenolsulphonephthalein as indicator.

4. Of the colloidal solutions used only an alcoholic extract of beef heart plus 0.2 per cent cholesterin, diluted 1:6 with physiological saline, was satisfactory.

The various reagents were employed in the following quantities:

Inactivated undiluted serum, 0.3 c. c.

Colloidal solution, 0.4 c. c.

Eight per cent NaCl solution, 0.6 c. c.

After these reagents were added, the tubes were shaken and incubated at 37° C. for 12 to 16 hours.

A known luetic and a non-luetic serum control were run with each series and each serum was controlled by replacing the colloidal solution by 0.4 c. c. of 15 per cent alcohol.

Two hundred sera were studied by this method and results compared with those of the Wassermann test on the same sera.

The following table shows the comparative results of the two reactions.

Wassermann reaction		Flocculation		
Results	Number	Present	Absent	Doubtful
*Positive	104	96	3	5
Suggestive Positive	5	5	0	0
Doubtful	19	14	1	4
Suggestive Negative	13	5	3	5
Negative	59	1	53	5

*** The terms positive, suggestive positive, doubtful, suggestive negative and negative, mean respectively 75 per cent to 100 per cent fixation, 50 per cent fixation, more than 25 per cent fixation, less than 25 per cent fixation and slight or no fixation.**

DISCUSSION

The results of the two reactions so closely parallel each other that it seems not improbable that complement fixation, as applied to the diagnosis of syphilis, may in some way depend on certain physical differences in the sera as shown by the increased flocculability of luetic serum in the presence of certain colloidal solutions.

This belief is further strengthened by the numerous attempts to apply complement fixation as a diagnostic method in diseases of man other than syphilis. These have so far proved entirely satisfactory only in yaws, a disease closely resembling syphilis in certain other respects. It must be admitted, however, that the short-comings of complement fixation, as applied to the diagnosis of diseases other than lues, may possibly depend upon other factors than the one suggested—the properties of the serum. In this connection may be mentioned the difficulties encountered in securing suitable antigens, that is, ones that are not anticomplementary in dilutions which show good binding strength.

It seems desirable to study the subject of complement fixation in the light of certain colloidal reactions and to determine its relation to these reactions, for there is evidence to support the belief that complement fixation may occur only

in the presence of two colloidal solutions (serum + antigen, or serum + antiserum) which react by the formation of a flocculus.

CONCLUSIONS

1. Syphilitic sera can be shown to differ from normal in certain physical properties.

2. This physical difference is possibly of fundamental importance in complement fixation reactions, although at present its relation to immunity reactions is not clear.

3. The Wassermann reaction and the flocculation reaction closely parallel each other.

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AN EXPERIMENTAL AND CLINICAL THERAPEUTIC STUDY OF WHOOPING-COUGH

By David I. Macht

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In a number of scientific communications published elsewhere, the author pointed out the interesting relationship existing between the chemical structure of the principal opium alkaloids and their pharmacological action on smooth muscle.[1] He has shown that these alkaloids can be sharply divided into two classes: the pyridin-phenanthrene group, of which morphin is the principal member, and the benzyl-isoquinolin group, of which papaverin is the principal representative. The morphin group is characterized by a stimulating action on smooth muscle structures, increasing their contractions and raising their tonus, while the papaverin group is characterized by a remarkable sedative effect on smooth muscle organs, tending to inhabit their contractions and to lower their tonus. It was further shown that the pharmacodynamic analysis of the papaverin effect pointed to the benzyl nucleus of the papaverin molecule as being responsible for the inhibitory and tonus-lowering action of papaverin and its related alkaloids. The reasons for these conclusions are to be found in detail in the author's papers. Following the above analysis of the papaverin action, the author described his search for and the successful discovery of a simpler compound containing the benzyl grouping and exhibiting the pharmacological properties of papaverin without its narcotic effects. It was shown that benzyl-benzoate actually produced all the pharmacological effects of papaverin on smooth muscle, but at the same time was much less toxic than that alkaloid on the other.[2] The therapeutic possibilities of benzyl-benzoate were then discussed and a series of clinical cases in which it had been used successfully were cited. The therapeutic indications for which the drug was recommended were those conditions of smooth muscle viscera which exhibited either an excessive peristalsis or excessive spasm, or both. Among such conditions were mentioned excessive peristalsis of the intestines, such as may be found in diarrhœa and dysentery, intestinal colic or entero-spasm, pyloro-spasm, uterine spasm, spasmodic conditions of the gall-bladder and of the urinary bladder, ureteral colic, angio-spasm, and others. The author is happy to state that all these indications for the use of and therapeutic application of benzyl-benzoate, which were predicted on the basis of his work some three years ago,[3] have been fully sustained and corroborated through further experimental and extensive clinical data gathered since.[4] Furthermore, certain new and unexpected therapeutic uses for benzyl-benzoate have been discovered which were not known to the author when he first published his work on the subject, and one of these he proposes to describe in the present paper.

Among the most interesting spasmodic conditions of smooth muscle organs, for which the use of benzyl-benzoate was originally advocated, is bronchial spasm or true asthma. The author, at the present time, has on hand the records of some 200 such cases, 75 per cent of which have been successfully treated with the drug.[5] Furthermore, he has received similar reports from various outside sources including a communication from Dr. W. Storm van Leeuwen of Holland, describing a series of some 60 cases in which it has been tried with a very high percentage of successful results. The author noted long ago that even in cases in which the asthma was not completely relieved by benzyl-benzoate, a sedative effect on cough was produced by the drug and the bronchial secretions were rendered more fluid. Inasmuch as the general indications for the use of benzyl-benzoate in therapeutics have been described by the author as "spasmodic" conditions of the viscera, a number of physicians through a rather fallacious process of reasoning, inquired whether the drug might not be useful in spasmodic conditions of the larynx, such as are characteristic of whooping-cough. *A priori*, the author did not expect much benefit to result from its use in such conditions, inasmuch as the muscles involved in laryngeal spasms are not of the smooth, but of the striated variety. Nevertheless, inasmuch as the pathogenesis and pathological

physiology of pertussis is not quite clear, and inasmuch as, according to some authorities, the condition is also accompanied by more or less bronchial spasm; and furthermore, inasmuch as the author had already noted some slight sedative effect after benzyl-benzoate in cough, a trial of the drug in whooping-cough was deemed worth while and the author studied its effects in a number of patients suffering from that disease. The results were so unexpectedly gratifying that a more extensive study was soon undertaken. This could be conveniently done in Baltimore during the summer of 1918 because, at that time, an unusually severe and widespread epidemic of whooping-cough was present in that city. Through the co-operation of Dr. John D. Hogan, Assistant Commissioner of Health in charge of Communicable Diseases, the author was able to secure a large number of cases of whooping-cough which he carefully treated with benzyl-benzoate and other drugs directly under his own supervision. In this paper, it is proposed briefly to summarize the results of the clinical observations made and to report some experimental data obtained in the laboratory dealing with the mode of action of the drug in whooping-cough.

The number of cases studied was about 115. Of these a few were in adults; but the vast majority were in children ranging in ages from a few weeks to fourteen years. Many of these cases occurred in groups of two, three or more in one family; and owing to the prevalence of the epidemic and its severe form, the diagnosis of whooping-cough, in most cases, could very easily be made. All these cases were characterized by whooping and in many the paroxysms were accompanied by vomiting and small hemorrhages. In a number of cases, a blood examination was made and gave the characteristic blood picture of pertussis. Most of the patients before coming under the author's observation had been treated by parents or doctors with paregoric and other popular drugs without any benefit, while others had been left alone without any treatment whatever. A number of the patients received vaccine treatment, but the results in these cases were also not at all striking.

When a study of the cases was begun by the author, all other medication was discontinued and the patients were given a 20 per cent solution of benzyl-benzoate by mouth. The dosage varied from 5 to 40 drops in water, three or four times a day and oftener, depending upon the age of the patient and the severity of the disease. In cases in which the simple alcoholic solution of benzyl-benzoate was found to be too distasteful to the young patients, it was flavored with a few drops of benzaldehyde and the medicine was administered in sugar water or milk. The author soon noted that the addition of a little benzaldehyde to a solution of benzyl-benzoate in amounts varying from 1 per cent to 5 per cent produced a mixture which seemed to act more effectively in cases of whooping-cough than benzyl-benzoate alone. A possible explanation for this is given below. It was found that the administration of benzyl-benzoate in the form of a suspension in simple elixir, in syrup of yerba santa and other syrups or elixirs was not a satisfactory method either of disguising the taste or administering the drug over long periods of time, as such mixtures are too bulky and unsightly and, in most cases, tend to disturb digestion even more than a benzyl-benzoate in alcohol would do in sensitive persons when administered without any flavoring.

The results of the clinical observations were as follows: About 90 per cent of all the patients showed more or less beneficial effects; about 50 per cent exhibited marked improvement in the symptoms. The therapeutic effects of benzyl-benzoate were not of a curative character but were of a distinctly palliative nature. These effects were manifested either by a reduction in the violence or in the number of paroxysms, or both; and also by the elimination of certain untoward sequelæ following violent whooping, such as vomiting, sub-conjunctival hemorrhages, lack of sleep, and emaciation. In many cases, the relief afforded by the drug was so marked that the parents came begging for more of the drug and recommended it also to their friends. Many of the patients who responded favorably to benzyl-benzoate had been previously treated unsuccessfully with bromides, antipyrin, quinin, belladonna, paregoric, and even heroin. In some cases, the author purposely interchanged or alternated the benzyl treatment with one or other of the above drugs, and the difference in the therapeutic effects could be readily noticed. Among such cases were three of the author's own children who were suffering with whooping-cough in a severe form. These patients were given all kinds of whooping-cough remedies, including heroin. None proved to be in the least effective unless given in toxic doses (heroin). On the other hand, when the children were given a solution of benzyl-benzoate plus benzaldehyde, a most remarkable relief in the violence of the paroxysms as well as a decrease in their number, was noted. Whether benzyl-benzoate has any effect upon the duration of the disease, it is at present impossible to say. It is doubtful whether the drug will have any influence on the cause of the disease but there is no doubt whatever, from the author's experience, that in benzyl-benzoate we certainly have a valuable palliative preparation and the value of such a drug, in view of the disastrous consequences of repeated and violent whooping paroxysms, needs no emphasis.

A very interesting question in connection with the effect of benzyl-benzoate on whooping-cough is: How does it act? To that end the author has been conducting a series of experiments during the past year and these experiments seem to indicate that the benzyl-effect in paroxysmal cough is exerted advantageously through a number of channels. The pathological physiology of whooping-cough is too complicated to be discussed in detail in the present paper; perhaps the best monograph on the subject is still that by G. Sticker in Nothnagel's *System*, to which the reader is referred. Briefly it may be stated that the two conditions which are conceded by all pathologists and clinicians to be present in whooping-cough are: (1) A catarrhal condition

of the larynx and other respiratory passages with a tenacious mucous secretion in the larynx; and (2) an excessive irritability or hypersensitiveness of the nervous mechanism of the larynx which readily induces a spasmodic contraction of the laryngeal muscles.

The pharmacological action of therapeutic doses of benzyl-benzoate in whooping-cough is apparently a manifold one. In the first place, the anti-spasmodic effect of the drug on bronchial spasm which very often accompanies the paroxysms, probably plays some rôle. Secondly, the author has conducted experiments in regard to the effect of benzyl-benzoate on the contractions of striated muscle and found that the drug is also a sedative for skeletal muscle though not, in the same degree, as in the case of smooth muscle.[8] In the third place—and this is probably of very great importance in the relief of the whooping paroxysms—the author found evidence that benzyl-benzoate probably exerts a slight anæsthetic effect on the larynx. It was found that the anæsthetic action so markedly exhibited by benzyl-alcohol, as described by the author elsewhere, is also exhibited in a high degree by benzaldehyde and to a lesser degree,[7] by benzyl-benzoate; and that both benzaldehyde and benzyl-benzoate when taken by mouth or even injected intravenously, are in part excreted in the saliva and the bronchial secretions. They therefore probably tend to diminish the sensitiveness of the otherwise excessively irritable mucosa of the larynx, and in that way prevent the vicious reflex which starts the paroxysms. Fourthly, the author has found through experimental studies on animals, as well as from clinical observations on patients, that the benzyl esters act as expectorants; and they therefore probably help to liquefy the tenacious clumps of mucus characteristic of whooping-cough, which are found in the larynx. Fifthly, the author has found from animal experiments and also from clinical observations that benzyl-benzoate is more or less of a sedative to the respiratory centre, and it would appear probable that this sedative effect upon the respiratory center is more marked in man than in the lower animals. Lastly, it is very possible that the antiseptic properties of benzaldehyde and benzyl esters[6] may play a rôle in combating the etiological factors of the disease.

It will be seen from the above considerations that the mode of action of benzyl-benzoate in whooping-cough is somewhat complicated. The effect of the drug in this condition is probably not a specific one, and indeed the author has used benzyl-benzoate with benzaldehyde successfully as a sedative in other forms of irritating spasmodic cough with viscid mucus.

As a result of a careful study of the cases treated by myself, I am inclined to believe that benzyl-benzoate, either alone or, still better, combined with a little benzaldehyde, is a valuable palliative or symptomatic remedy in pertussis. It is, of course, well known that in practical therapeutics, no measure will give a 100 per cent of successful results, so that a trial of the above treatment by other observers is very desirable. I should like especially to emphasize the very low toxicity of benzyl-benzoate, which would warrant its administration in even larger doses than those at first recommended. The dose of the drug to be employed will have to be determined by the physician in charge of each case. Thus, in a small series of about 30 cases of whooping-cough treated at my suggestion by officers of the Health Department of another city, the results obtained were much less promising than in my own cases, but later experience has convinced me that much better results would have been obtained had the dosage been somewhat larger than that recommended originally in this series of cases. On the other, hand, reports from other sources seem to sustain my own original favorable experiences. More complete data of the experimental work in connection with this investigation and also further clinical experiences will appear in the Journal of Pharmacology and Experimental Therapeutics.

CONCLUSIONS

1. The administration of benzyl-benzoate solution alone and still better, in combination with small doses of benzaldehyde, exerts a beneficial palliative effect on the violence and number of whooping-cough paroxysms.

2. The mode of action of the drug in such cases has been investigated experimentally and is discussed in the text.

3. In view of the low toxicity of benzyl-benzoate and benzaldehyde, and the considerable number of successful therapeutic results obtained with them, their further trial in the symptomatic treatment of paroxysmal cough and especially of whooping-cough is deemed advisable.

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THE PIGMENTED EPITHELIUM OF THE EMBRYO CHICK'S EYE STUDIED *IN VIVO* AND *IN VITRO*

WITH SPECIAL REFERENCE TO THE ORIGIN AND DEVELOPMENT OF MELANIN PIGMENT

By DAVID T. SMITH

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INTRODUCTION

The term *melanin* has been given to a varied and complex group of pigments which give the color to the hair, eyes, and skin in man, and are also responsible for the color of most of the birds, animals, and insects (Gortner, 1911). According to Gortner, the melanins may be divided into at least two classes: (1) The melano-proteins, which are soluble in dilute acid but not in ordinary organic solvents; when hydrolized with strong acids these yield tyrosin, lysin, arginin, and an unidentified brownish black residue. Pigment of this type is found in auburn hair, appearing as a diffuse color and not in the form of granules. (2) The melanin proper, which is the more abundant type, occurs generally in the form of small granules. It is not soluble in dilute acid or in any of the usual solvents.

It is generally believed that pigment is produced by the action of an oxidase on an oxidizable chromogen (Gortner, 1911). This oxidase is called *tyrosinase*, because of the fact that it acts on tyrosin and other aromatic compounds containing a hydroxyl group (Bertrand, 1896, 1908). Its reaction is supposed to produce a melanin-like pigment; indeed, von Furth and Schneider (1901) were able to isolate a tyrosinase from the hemolymph of Lepidopteran larvæ which, when treated with tyrosin, produced a black pigment. This artificial melanin had all the chemical properties of natural melanin; on analysis it gave practically the same proportions of carbon, nitrogen, and hydrogen as had been obtained from the melanin pigment of the negro skin (Abel and Davis, 1896). Gessard (1903) found tyrosinase in the ink-sac of the cuttlefish and in melanotic tumors of the horse. In fact, it has been found by various investigators to be widely distributed in tissues where it may give rise to melanin by an oxidation of the chromogen (Kastle, 1909).

The nature of the oxidizable chromogen has received quite as much attention as the oxidizing agent. Von Nathusius (1894) found that when white hair was subjected to boiling in aqueous solution of methyl-green, minute, deeply colored particles could be seen which corresponded in size and position to the pigment granules in black hair. He therefore concluded that the same histological element is present in both white and black hair, except that in the former it is colorless. Abel and Davis (1896) found that the pigment granules of the negro's skin and hair could be partially decolorized by heating with ammonia and alcohol and that they would then stain strongly with gentian violet.

In 1889 Mertsching proposed the theory that melanin was formed by the breaking down of the cell, especially of the nucleus. Rossle (1904), studying pigment formation in melano-sarcoma, came to the conclusion that pigment was produced by the extrusion of small particles of nuclear material and that the nucleus was impoverished thereby. Schultz (1912) studied a case of mycosis fungoides and he, too, decided that the oxidizable chromogen is derived from the nucleus. Aurel von Szily (1911) observed the formation of melanin pigment in the developing eye of a variety of vertebrates, including the hen, and also described pigment formation in melanotic tumors of the human eye. He concluded that the pigment came out of the nucleus as colorless, rod-shaped granules, which later became colored as they wandered about in the cytoplasm of the cell, probably by the action of cell ferments. This coloring did not take place simultaneously in all parts of the granule, but began at one end and proceeded to the other. The production of pigment took place with or without degeneration in the nucleus.

Dyson (1911) held the theory that the pigment is developed from a lipochrome which he believed to be a product of the nucleus. Certain other observers have been unable to find any evidence that the granules come from the nucleus and believe that they develop from the mitochondria. Champy (1911) denied their nuclear origin and described thread-like mitochondria breaking into fusiform granules that were at first colorless but later became colored. He was the first observer to note that the granules appeared to collect about the centriole (Nebenkern). Leplat (1912) did not observe any definite arrangement about the centriole, but he, too, believed that the pigment was probably derived from the mitochondria. The same conclusion was reached by Luna (1913) who studied melanin pigment in the eye of embryo frogs and chicks.

Strong (1902) advanced the theory that the pigment granules arise within the cytoplasm of the cell and gave a detailed study of the fundaments of the feather showing this to be the case. He stated that "the pigment arises in the form of grayish or light yellow corpuscles of exceedingly small size, arranged along delicate protoplasmic strands which radiate from the nucleus." He does not mention the centrosphere but some of the drawings, as well as the photographs, given in his paper show the pigment granules arranged at one side of the nucleus around what is undoubtedly the centrosphere.

Hooker (1915) began his investigations of the subject with the tissue culture method. He studied the melanophoric cells of the frog larvæ cultivated in plasma and observed the formation of pigment, but found no evidence that it was derived from nuclear substance, nor did he see any signs of the colorless granules described by von Szily. He concluded that the pigment was formed from material in solution in the cytoplasm, and that the nucleus was active in the production of an oxidase which acted on this soluble chromogen. In 1917 Luna cultivated the pigment epithelium of the eye of embryo chicks in plasma, but was not able to find any evidence that the mitochondria changed to pigment in the cultures. He still contended, however, that such a change might take place in the living embryo.

It will be seen from this brief review that the theories concerning the origin of the pigment granules are decidely at variance, different authors claiming respectively that their source is (1) the nucleus, (2) the mitochondria, and (3) the cytoplasm.

I wish to acknowledge the valuable assistance and encouragement of Mrs. Lewis and Prof. W. H. Lewis, in whose laboratory these observations were made.

TECHNIQUE

The pigment layer of the retina of the chick embryo (5 to 15 days' incubation) was chosen for study. The tissue was removed and pieces of it explanted in Locke-Lewis solution according to the method employed by Lewis and Lewis (1915). Other explants were made in plasma by the Burrows (1910) method. Film preparations were also made by placing a piece of the pigmented layer in a drop of Locke-Lewis solution and covering it with a coverglass. If just the right amount of fluid is extracted from under the coverslip the pressure caused by the weight of the coverslip spreads the cells out thin and thus they can be observed with advantage under the microscope. Fixed and stained preparations, made from both the cultures and the films, were studied for a comparison with the methods of other observers. The living cultures were stained with neutral red and janus green. One series of cultures were grown in Locke-Lewis solution containing neutral red; after the pigment granules had taken up the red stain, a number of these cultures were fixed in Zenker's fluid from which the acetic acid had been omitted and stained with iron hematoxylin. Zenker's without acetic acid was used most frequently as the fixing agent. Various preparations were stained with iron hematoxylin, crystal violet, safranin, anilin fuchsin, aurantia, toluidin blue, and eosin.

These methods were followed in order to observe directly, if possible, whether the mitochondria change into pigment granules or whether the granules arise independently in the cytoplasm, and also to see what changes in color, size, and shape take place in the granules during their development. Furthermore, if the granules were extruded from the nucleus, as described by some investigators, I concluded that it should be possible to observe the process under the microscope.

OBSERVATIONS

In order to get an adequate idea of how the pigment cells of the living retina appear unstained, film preparations were made. The eye of an eight-day chick embryo was removed and dissected, the pigment layer being stripped off carefully from the underlying choroid. Films were then made from the pigment layer and studied with an oil-immersion lens. A membrane of rather large hexagonal cells was found; the nuclei could be made out distinctly, but the remainder of the cytoplasm was densely packed with dark brown or black rod-like granules. On this account no mitochondria could be seen.

Another egg was opened, the pigment layer of the retina peeled out, and tiny pieces were explanted by the Lewis method. In five or six hours connective-tissue cells from the choroid began to grow out. In one case retinal cells also appeared, but usually the pigment cells were not observed before fifteen to thirty hours.

Along the free edge of the cell clear protoplasm was seen to flow out (Figs. 1 and 2), forming a transparent border in sharp contrast to the black pigmented body of the cell. This protoplasm at first contained neither pigment granules nor mitochondria. The advancing protoplasm put out processes along the under surface of the coverglass after the manner of amœbæ, although much more slowly. When an obstacle was encountered or the temperature became unfavorable, these processes were rather rapidly withdrawn; however, in their retreat they left enough of their substance on the coverglass, in the form of a slight smear, to reveal where they had been. After the processes had moved out a convenient distance, they seemed to anchor themselves to the glass and to draw outward bodily the remainder of the cell. This procedure was repeated until the proximal part of the cell was pulled out from the original mass. The migration was relatively slow and generally took several hours for its completion. The migrating cells were not separated entirely from the original mass; each one was connected with the cell immediately behind and with the one on either side, so that when the first moved out it drew the other three after it. These cells in turn repeated the process until a membrane of cells was formed (Fig. 1).

In one culture the cells did not grow out in the membrane formation just described, but were joined to one another by their ends like connective-tissue cells. Luna (1917) described and figured both types of growth. The cells that were farthest from the original piece were very thin and spread out over an area two to two and a half times as large as that occupied by the original cell. Those nearer the explant approached nearer the dimensions of the original cells. The thin cells on the periphery were used for study.

There was little difference observed between refraction of the nucleus and that of the cytoplasm. Most of the granules were concentrated into a large mass at one side or one end of the nucleus (Fig. 2), probably about the centriole or centrosphere, in much the same manner as the degenerating granules

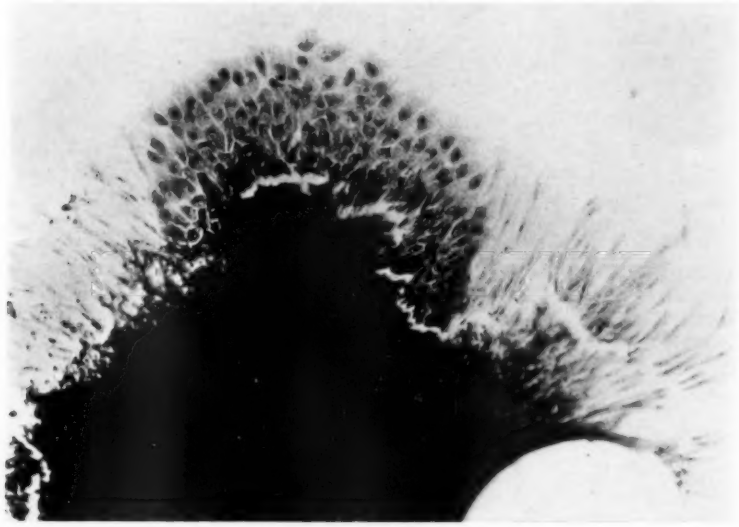


FIG. 1.—Photograph of a 72-hour growth from the pigment layer of the eye of an 8-day chick embryo in Locke-Lewis solution. The darker membrane is the growth of pigment cells. The spindle-shaped cells on each side are fibroblasts. The growth broke away from the explant when mounted.

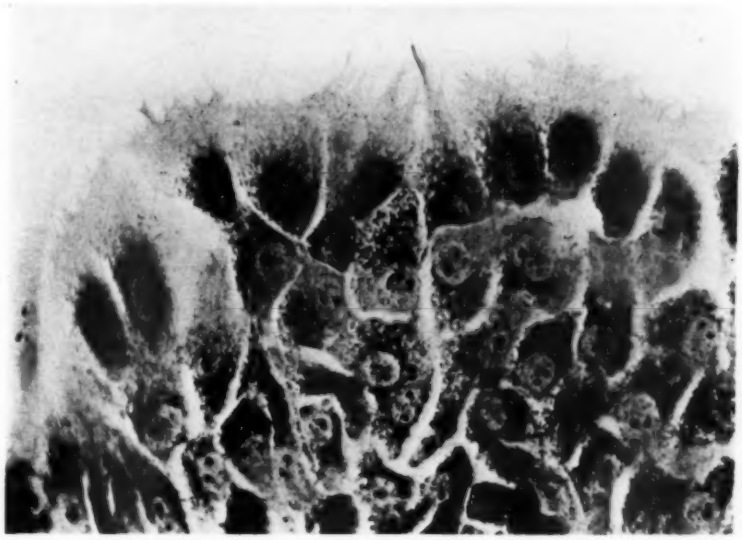
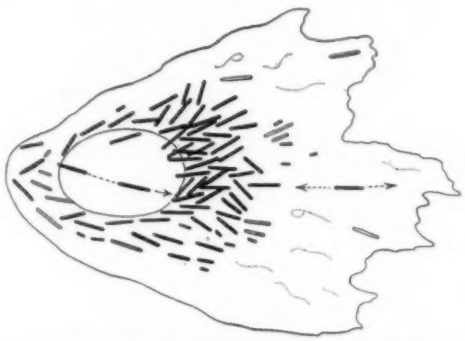


FIG. 2.—A photograph taken with a higher magnification (× 550) of the left area of the pigment epithelium shown in Fig. 1. In most of the cells the pigment granules are massed around the centrosphere at one side of the nucleus.

and vacuoles observed in fibroblasts by W. H. Lewis (1919). From this mass granules extended out in all directions and in some cells surrounded the nucleus. Schmidt (1917) also observed this phenomenon. The nucleus and the mass of granules occupied the proximal three-fifths of the cell. The distal two-fifths was composed of relatively clear cytoplasm in which mitochondria and scattered pigment granules could be seen (text fig.). The mitochondria were generally in the form of filaments or rods and were seen to move slowly about in the cytoplasm. The pigment granules were usually plump rods, the length varying from one and a half to five times their width. Nearly all the cultures contained a few perfectly round ones also, the number being greater in some cultures than in others. The larger granules were estimated to be from two to three times as large as those found in the human skin. In color they were for the most part between dark brown and black, although various shades of gray could also be seen. The great majority of the granules were of maximum size and black in color. Regardless of the shade, however, the color of each individual granule was homogeneous.



TEXT FIG.—A diagrammatic representation of a cell from the growth of pigment epithelium, showing the various types of pigment granules found at different stages in the development of the pigment. The thin threads are the mitochondria. The stippled granules represent the gray pigment granules while the clear and the black bodies are intended to show the different sizes and shapes of the colorless and black pigment granules.

When the culture is first placed under the microscope the pigment granules show little signs of activity, but under the influence of light and heat their movement is accelerated. They move in the cytoplasm with a swift, jerky motion, starting off with a jump, going a little way, stopping suddenly for a second or two, and then starting off with another spurt. Some of them show a tendency to move in definite paths back and forth from a point near the nucleus to the periphery. Sometimes this journey is made with only the one stop at the periphery; at others it is accomplished by a series of spurts. When the granule reaches the periphery it may or may not reverse ends before coming back. It is estimated that at the minimum it required about 3 seconds to reach the periphery, 2 seconds to reverse or rest, and 3 seconds to return. Some granules move about in the cytoplasm in an apparently aimless manner. When in motion the granules may strike the mitochondria, bend them aside, and go in; in fact, a pigment granule may plough through a relatively thick mass of mitochondria.

The granules were found to migrate much farther out into the peripheral processes than do the mitochondria. They have also been observed to move entirely across the nucleus. Those which in Fig. 2 appear to be in the nucleus were actually in the cytoplasm between the nuclear and the cytoplasmic membranes.

In all of the cultures some granules were observed to be free in the culture fluid. This was due to the destruction of a certain number of pigment-bearing cells in the process of explanting the tissue. In cultures planted in Locke-Lewis solution these free granules underwent Brownian motion. Each culture contained also a certain number of blood cells carried over with the explant from the ruptured vessels of the choroid. The red blood cells, all of which were of course nucleated, showed no tendency to take up the loose granules. The clasmatocytes, on the contrary, did so readily and sometimes appeared quite black with granules. Some of the connective-tissue cells also took up the pigment granules, but this phagocytosis was more limited in extent than that in the clasmatocytes, rarely more than three or four granules being ingested by a single cell. They appeared usually to be taken directly into the cytoplasm and not into vacuoles. Some were seen to move in the cytoplasm of these connective-tissue cells, but their motion was not characteristic nor was it anything like so extensive as in the epithelial cells.

A peculiar change took place in some of the granules that had been taken up by the connective-tissue cells; they appeared to swell up and there was a relative if not an actual decrease in color. Whether the process would have gone on until there was a complete decolorization of the granule was not determined. Such decolorization did not take place in the granules of the pigment epithelium grown in Locke-Lewis solution, even when incubated as long as a month.

When neutral red was applied to a culture it was found that the pigment granules took the stain. The longer the stain was allowed to act, the deeper was the color. When a little neutral red was added to the culture medium and the cells were grown in it, the granules became decidedly red. Furthermore, even after such a culture was fixed in Zenker's fluid (without acetic acid), cleared, stained with iron hæmotoxylin, and mounted in balsam, the granules still retained the red color. In some specimens it was still marked at the end of nine months. The gray granules seemed to take the red even better than the black ones. When a combination of neutral red and janus green was applied to a culture it brought out the mitochondria and the pigment granules in sharp distinction. The mitochondria stained bright blue with the janus, while the pigment granules took up the red. Lewis and Lewis (1915), W. H. Lewis (1919), and others have shown that the neutral red does not stain the mitochondria. They have also shown that the "neutral red bodies," which take the red in the living cell, lose their color on the death of the cell. Hence, so far as we know, only the pigment gran-

ules are capable of keeping the neutral red stain after fixation and mounting. This staining reaction offers, therefore, a simple method by which the pigment granules can be differentiated from other cellular elements. The peculiar pigment granules described above in certain of the connective-tissue cells failed to stain with janus green but stained quite readily with neutral red.

The age at which degeneration begins in cultures grown in Locke-Lewis solution cannot be given accurately, as it may range from 24 hours to 5 days. It can be brought about at any age by allowing the temperature of the warm box to rise from 39° to 45° C. The first sign of degeneration is the formation of tiny vacuoles in the cytoplasm, accompanied by changes in the mitochondria, some of the filaments breaking up into short rods and forming tiny vesicles. The vacuoles increase rapidly in number and in size. A few fat droplets also appear in the cytoplasm. After the vacuoles have reached a fair size, blebs are seen to form in the wall of the cytoplasmic membrane. From this stage on the nucleus becomes more and more refractive. The blebs contain a fluid that has a different index of refraction from the cytoplasm. At first they change in size and shape with a fair degree of rapidity, but later become more stable. Pigment granules are often drawn into these blebs, and when this occurs the granules lose their characteristic movement and exhibit Brownian motion. The process continues until the cytoplasm is a mass of vacuoles; the nucleus then begins to break up, the cell loses its definite outline and the vacuoles themselves break up. Strange to say, however, the pigment granules are not destroyed by these reactions. I found them holding their size, shape, color, and relative positions, although spread out over a larger area. It is possible to estimate from them the size and shape of the obliterated cell, very much as one would estimate the size and shape of a man from his skeleton. The time required for the completion of the degenerative process may range from 24 hours to a week or more.

Control cultures made in plasma gave practically the same picture of growth and degeneration.

Luna (1917) studied the pigment cells exclusively in plasma cultures, and gave an excellent description of their normal growth, which is essentially the same as the above. He claimed that no mitotic division took place but described what appears to have been direct division in a few cells that became detached from the growth and were in the process of degeneration. Uhlenhuth (1914) found no division of any kind in the pigment epithelium of the frog's retina. In the author's investigations, likewise, no division of the cells was observed.

A more detailed consideration of the various intracellular structures, *i. e.*, mitochondria, pigment granules, neutral red bodies, and fat droplets, together with their relation to each other, is given below.

MITOCHONDRIA

The mitochondria could be carefully studied in the thin peripheral cells. They occurred mainly as filaments and rods and appeared to be slowly wafted about in the cytoplasm of the cell by intracellular currents (?). The filaments were seen to bend on themselves, forming triangles, circles, loops, and corkscrew forms, but these later straightened out again or changed to some other figures. Although cultures were observed continuously for hours at a time, absolutely no indication of the mitochondria being changed into pigment granules was seen. Luna reported similar results from his observations. The mitochondria were stained in the living cell with janus green. Cowdry (1914) and Lewis and Lewis (1915) as well as others, have shown that janus green colors the mitochondria and differentiates them from the cytoplasm and from the other cellular elements. In my observations the janus green stained the mitochondria a bright blue, but uniformly failed to stain any granule that had a particle of brown or black in it.

As noted above, Luna (1917) assumed that the mitochondria might turn into pigment granules in the eye of the living embryo, although he failed to observe that they did so in his cultures. To test this point the author made fresh spreads of the pigment layer taken from the eye of living embryos of 3 to 5 days' incubation and stained them with janus green. These ages were chosen because it had been previously determined that pigment production was most active at this time. None of the granules that had any color, or even the characteristic rod shape, took up the stain.

MELANIN PIGMENT GRANULES

The general appearance and behavior of pigment granules in cultures have been described above. In view of the various theories as to the origin of these granules, it was deemed of interest to determine at what hour of incubation and in what form they first appear in the cell. Accordingly, series of preparations of embryos ranging from 5 days down to 42 hours of incubation were made with the aid of a dissecting microscope. In embryos of 3 to 5 days' incubation the optic vesicle was opened and the pigmented epithelial layer of the retina teased out. Small pieces were studied fresh and also after fixation in Zenker's fluid without acetic acid. The fresh material was stained with janus green and neutral red and studied in a warm box. In the fixed material small pieces of the pigmented tissue were transferred in a pipette to a coverglass and the excess fluid was removed with a pipette. A drop of Zenker's fluid, without acetic acid, was placed on a slide, and carefully covered with the coverslip, the cells being flattened out by gentle pressure on the coverslip. The preparation was then sealed with vaseline to prevent evaporation. The fixing solution was allowed to act from two to four hours. The length of time necessary for good fixation was determined by the appearance of the tissue under the microscope. After fixation the vaseline was removed and the coverslip separated from the slide, the tissue usually adhering to it. The preparation was then cleared by the usual method. This treatment gave good results because the pigmented membrane was composed of a single layer of cells. For prepara-

tions between 3 days and 42 hours the whole eye was teased out into tiny pieces after it had been transferred to the coverglass. It was then fixed in Zenker's and carried through the procedure described above. One such series was mounted unstained in order to get the variations in the color of the granules at the different ages. Other series were stained with various dyes as will be described farther on.

At 42 hours the optic cup is not yet invaginated. The pigment-bearing cells, by reason of their large-sized, characteristic, large, round nucleus, and a relatively small amount of cytoplasm, could be readily distinguished from the cells that were to form the visual elements. A few of these pigment cells exhibited signs of granules. An occasional gray or colorless granule of small or medium size was seen, but none were found that were black when exposed to the full light of the microscope; neither were there any that could be called full grown. Neutral red was applied as a vital dye to one such preparation and after staining had taken place the tissue was fixed in Zenker's. The granules that contained some black and those that appeared colorless both took the red. In addition, small red granules could be seen that were invisible before. This would indicate that these granules were of the same material as the larger ones.

In a 48-hour embryo the circulation is very active. An unstained specimen of this stage showed an increase in the number of grayish black granules, although none of them were as yet of maximum size and color. Staining with neutral red showed that there was a considerable increase in the number of the small red granules.

In the eye of a 60-hour embryo some of the medium-sized granules and some very small ones were found to be black even when exposed to the full light of the microscope. As in the younger embroyos, various shades of gray were seen. The neutral red brought into evidence a large number of the small red ones, many of which were in the form of plump rods.

At the 66-hour stage the retina contained a few granules of maximum size and color. Wide variations in color were noted; some of the smallest granules were dark while some of the medium-sized ones were almost colorless. Neutral red gave the same picture as that mentioned above.

An unstained preparation from the eye of a 72-hour embryo showed a considerable increase in the number of black granules of all sizes. One of the fixed specimens was stained with an alcoholic solution of crystal violet. The entire cell took the stain diffusely but the granules were stained more deeply and stood out quite well, even the very small ones being visible. Some of these were even a little smaller than those demonstrated with the neutral red. Toluidin blue also stained the granules but not so well as the crystal violet.

The 78-hour specimen showed the same picture but more advanced. Each cell contained from 10 to 25 granules, including a number of small black ones. Aurantia, toluidin blue, and crystal violet all stained the granules.

In preparations of a 96-hour embryo the granules appeared to have about doubled in number in the preceding 18 hours. The variations in size and color were practically the same as recorded above.

At 120 hours the granules had increased to such an extent that it was impossible to count them. There was a much larger proportion of medium and larger sized ones than were found in younger stages. There remained, however, more of the small and the gray granules than are present in the fully developed eye.

In not one of the series was there any indication that the granules were extruded from the nucleus. The nuclear membrane appeared always intact. The granules, so far as it was possible to tell by simple observation, were always in the cytoplasm and never in the nucleus.

It was thought that signs of pigment production were detected in cultures made from embryos of 5 to 15 days, but this could not be determined accurately because of the large number and active movement of the granules. Accordingly, cultures were made from the eye of 2-day chick embryos, at which stage the granules are small and few in number and are not of maximum blackness. Because of the very small size of the eyes at this time only one explant could be made from each. Hen plasma, Locke-Lewis solution, and a mixture of the two were used respectively as culture media.

The cells did not exhibit amœboid motion and did not grow out, but along the edge of the tissue individual cells were found that were thin enough to allow accurate observation. After 4 days' incubation there was a slight but definite increase in the number, size, and depth of color of the granules. Nevertheless, we must conclude from these, as from previous experiments that pigment production is not active in tissue cultures.

It may be noted that in some of the preparations crystal violet was used to stain the pigment granules. It is well known that crystal violet is used in the Benda method as a mitochondrial stain. This does not indicate, however, that the granules are of mitochondrial substance, as will be seen by the following experiments.

A few pigment-bearing cells were spread out on a slide. The cells were broken up to a great extent, leaving many of the granules free on the slide like bacteria. The preparation was then stained with an alcoholic solution of crystal violet. The granules, which in the fresh material appeared as dark brown or black, were now tan in color. On the other hand, the granules that had appeared gray or colorless in the fresh were violet in color. These varied in size from the usual pigment granule down to the limits of visibility. Several of these smears were made and all gave the same result. One of them was treated with cold concentrated HCl for two hours. The color of the stain was removed by the acid, but when the smear was restained the pigment granules, from the largest down to the smallest, were found to be intact. The cell outlines had partially disappeared and what remained had changed to a homogeneous, blue-staining mass. Some of the granules that before had looked dark tan, now appeared purplish. The acid experiment was repeated several times

with intact cells that had been previously fixed in Zenker's. Sometimes the cell outlines were not entirely destroyed, but the nucleus and the cytoplasm were reduced to a bluish-staining mass in which could be seen the intact pigment granules of various sizes. In cells from the choroid, used for control, these small, purple-staining granules could not be found. Since neither the large nor the small pigment granules were affected by the HCl, whereas mitochondria are destroyed by weak acetic acid, we must conclude that these two cellular elements are probably different chemically.

The exact chemical structure of the pigment has not been determined. Hirschfeld (1889) found the pigment granules in the eye of the ox to be composed of a protein stroma and a dark brown amorphous pigment. His analysis of the pigment showed neither iron nor sulphur. From this he concluded that it was not a derivative of hemoglobin. His conclusion as to the absence of iron has been supported by Abel and Davis (1896) and a host of other chemists. Abel and Davis found that the pigment granules of the negro's skin and hair could be separated into a colorless protein stroma and a dark brown amorphous powder by treating with HCl, followed by boiling in weak alkali for a considerable length of time. The pigment was found to contain sulphur but no iron.

Repeating the work of several investigators, I decolorized these granules with hydrogen peroxide and potassium permanganate. After this process the granules still retained their size, shape, and general appearance except for the loss of color; they could then be stained with any of the stains mentioned above.

NEUTRAL RED BODIES

The neutral red granules that have been described in tissue cultures by W. H. Lewis, are few in number or entirely absent in normal young growths of retinal cells. They appear and increase in number with the age of the culture but are never seen in the pigment cells to the same extent as in connective-tissue cells growing in the same culture. There is little danger of confusing the small, colorless pigment granules with the neutral red bodies for the following reasons: (1) The colorless pigment granule is present in the cell before the neutral red granule makes its appearance. (2) The tiny pigment granules usually have a uniform rod shape with an index of refraction that is slightly different from that of the neutral red body. (3) The pigment granule, when stained, holds its red color even after fixation and mounting, while the other type of granule disappears at the death of the cell.

FAT DROPLETS

The amount of fat found in these cells varies with the condition of the culture and with the nature of the medium. Cultures grown in Locke-Lewis solution contain very little fat. Practically no visible fat is found in young cells grown in this medium, but as the cells degenerate some fine globules make their appearance. These can be stained with Sudan III. If the cultures are grown in plasma from a fat hen, even the young cells are found to contain quite a number of large fat droplets which have evidently been absorbed from the plasma (Lambert, 1913). A study of the living pigmented epithelial cell did not show any connection between the pigment granules and the fat globules. So far as could be seen, the fat globules present in the cell took no part in the formation of the pigment granules, neither were the pigment granules in any way related to the formation of the fat globules.

DISCUSSION

In the introduction it was noted that some workers hold the theory that the pigment granules arise from the nucleus, others, that they are derived from the mitochondria, while Hooker believes that they originate in the cytoplasm. Aurel von Szily (1911) is one of the foremost of those who consider the nucleus responsible for the granules. His results are the more readily compared with my own because a part of his work was done on the embryo chick's eye. He stated that pigment production may take place with or without degeneration of the nucleus. He described the nucleus as extruding a colorless granule which became colored as it wandered about in the cell, the coloration beginning at one end of the granule and proceeding to the other. He gives numerous figures to illustrate this process.

Certainly in my own series I found no signs of nuclear degeneration. That there are colorless granules in these cells during the stage of active pigment production is confirmed by the observations herein recorded, but the results do not lend support to von Szily's theory as to the process of coloration. With the idea of determining this point hundreds of granules of various shades were examined carefully, and in every instance the granule was found to be homogeneous in color. In justification of von Szily, it may be said that at first sight many of the granules appeared to be black at one end and light at the other. Sometimes this was found to be due to the fact that they were viewed from an angle, in which case the end which was in focus was black while the end that was slightly out of focus appeared gray. By careful focusing, the black could be made to move from one end of the granule to the other, showing that it was really black in color throughout. At other times the appearance of one black end was due to an overlying or crossing of the granules at various angles. No granules were ever observed in the nucleus, although often they were seen to move over the surface of the nucleus and on out into the cytoplasm. In fixed preparations many of these granules undoubtedly appear to be coming out of the nucleus. It is possible that this is what von Szily has described. His final point in favor of a nuclear origin is the fact that the granules stain with a nuclear stain. This is true; but they likewise stain with cytoplasmic stains. Schultz (1912), who supports the nuclear theory, describes small pigment granules in the cytoplasm some of which stain with eosin and others with basic dyes. I am inclined to believe that the proof offered for a nuclear origin of the pigment granules is not conclusive, at any rate in the chick.

Those who support the mitochondrial theory base their conclusions largely on the following observations: (1) There is a similarity in appearance between certain of the mitochondrial forms and the small gray or colorless pigment granules. (2) They give a similar staining reaction with certain stains. (3) The mitochondria are supposed to disappear as the pigment granules appear in the cell.

1. It is fair to assume that if there is any change from mitochondria to pigment granules such transition would be from the mitochondria to the least differentiated form of the pigment series, which happens to be the small, colorless granule. My own investigations afford the following evidence against such a theory: (a) These colorless pigment granules are not so refractive to light as the mitochondria; (b) in an extensive study of the mitochondria in the living cell no change to pigment granules was detected (Luna, 1917, records a similar result); (c) films made from the eyes of embryos during the stages of most active pigment production and stained with janus green and neutral red, gave no indication that the mitochondria were being changed into pigment; (d) these small granules have the shape and the characteristic jerky movement of the larger pigment granules and nothing of the slow drifting motion of the mitochondria; (e) the colorless granules are much more stable than the mitochondria—they are not destroyed by acetic acid nor even by concentrated HCl.

2. In regard to the reported results that the colorless granules stain like mitochondria, my observations yielded contradictory evidence. While it may be true that after fixation these granules stain with certain dyes just as do the mitochondria, it does not necessarily follow that they are the same structure. Duesberg (1910) states that, although certain structures in the spermatid of Blatta Germanica stain like the mitochondria, they are in all probability not mitochondria. This heterogeneous staining is well known in connection with many of the usual histological methods. Fortunately, we are not dependent upon fixed tissue stains alone for the determination of this point. In the living cell these colorless granules are not stained by janus green, which is recognized as a specific mitochondrial stain (Cowdry, 1914; Lewis and Lewis, 1915). They stain readily with neutral red which Lewis (1919) has shown does not stain the mitochondria in the fibroblasts of tissue cultures. Their physical appearance and behavior, their resistance to strong acid, and their staining reactions identify the colorless granules with the stroma of the larger granules which is known to be very different chemically from the mitochondria.

3. If the mitochondria do actually disappear as the pigment increases in the cell it can be readily seen that this would be an important point in favor of the mitochondrial theory. As shown by his figures, Luna (1917) found numerous mitochondria in cultures of retinæ of the same ages as those from which he had previously (1913) drawn the conclusion from a study of fixed material that the mitochondria had disappeared with the advent of pigment formation. In our cultures the cells of the pigmented membrane contained about the same amount of mitochondria, regardless of the embryonic stage or the amount of pigment present in the cell. The natural conclusion from this is that the mitochondria do not decrease with the increase of pigment.

Hooker's conclusion that the granules arise in the cytoplasm of the cell comes nearer to fitting the known facts, although he did not find colorless granules in the epithelial cells of the frog. He holds the view that an oxidase acts on a soluble chromogen and produces a black pigment. This may be correct for the frog, but in the chick's eye it is evident that the process may take place in two distinct stages: (1) The formation of a colorless chromogen, which is shown by the presence of colorless granules in the younger stages of development; (2) the production of color in this chromogen, probably by the action of cell ferments. This is shown by the various shades of gray found among these granules and by the fact that the gray ones have practically disappeared from the fully developed eye. In general it may be said that these two processes go on at the same time. Hence we get a small black granule in the cytoplasm which grows by accretion (?) into a large black granule. That the granules actually grow in the cytoplasm of the cell is shown by the fact there is a gradual change from a large number of small granules and relatively few large ones in the younger ages to a large number of "full grown" granules and only a few small ones in the fully developed eye. This gradual increase in the size of the granules with the age of the embryo is recorded by Luna (1913, 1917). Furthermore, granules have been seen to increase in size in cultures made from the eyes of 2-day chick embryos.

CONCLUSIONS

1. Tissue culture affords an excellent method for the study of the pigmented cells in the retina of the chick. The pigment cells migrate out on the under surface of the coverglass and spread out in the form of a thin membrane, thus offering an excellent opportunity to observe the behavior of the different granules found in their cytoplasm.

2. No cell division of any kind was observed in these cultures from the pigmented layer of the retina.

3. The production of pigment in tissue cultures is limited in extent.

4. The pigment granules are very stable. Even the small colorless and small gray ones are not destroyed by cold concentrated HCl.

5. The pigment granules move in the cytoplasm of the cell with a swift, jerky motion, which is much accelerated by continuous exposure to light.

6. They tend to concentrate about the centriole or centrosphere and to move in radiating paths between the centriole and the periphery, or vice versa.

7. When the cells are grown in a medium that contains neutral red, or when exposed to its action for a considerable length of time, the pigment granules stain with neutral red and retain it even after fixation. Other granules in these cells may take up neutral red but these lose it on fixation.

8. In fixed material the granules were found to stain with either basic or acid stains.

9. The pigment granules did not appear to be either derived from or changed into fat.

10. The pigment granules were not observed to be extruded from the nucleus.

11. There was no evidence that the mitochondria changed into pigment.

12. So far as could be determined from these observations, the granules arise and develop in the cytoplasm of the cell. The first signs of pigmentation were found at the stage of 42 hours' incubation. A few small colorless and small gray granules were seen in the cytoplasm of the cell at this age; these gradually increase in size, number, and depth of color until the cell becomes full of black, rod-shaped granules (17 days). There are at least two stages in the process of pigment production: (a) the formation of a colorless chromogen, followed by (b) the production of color in the chromogen. These processes generally go on simultaneously, but the chromogen may be laid down faster than the coloring takes place. This is shown by the presence of colorless granules in the younger ages.

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PROCEEDINGS OF SOCIETIES

THE JOHNS HOPKINS HOSPITAL MEDICAL SOCIETY

MARCH 1, 1920

1. The Distribution of Adenomyomata Containing Uterine Mucosa.* DR. THOMAS S. CULLEN.

The following is a short abstract. The paper in full together with illustrations will appear in an early issue of the American Medical Association's new surgical journal—*Archives of Surgery*.

*Address in Surgery before the Western Surgical Association, Kansas City, Mo., December, 1919, and before The Johns Hopkins Hospital Medical Society, March 1, 1920.

"At the Johns Hopkins Medical Society's meeting in March, 1895, I reported my first case of adenomyoma of the uterus and ever since then have been on the lookout for tumors of this character. From time to time the results of our labors have been recorded either in book form or in the literature.

"I have been amazed at the widespread distribution of these tumors consisting of non-striped muscle with islands of uterine mucosa scattered throughout them.

"Adenomyomata containing uterine mucosa have been found in the following locations: 1. Adenomyomata of the body of the uterus. 2. Adenomyomata of the rectovaginal septum. 3. Adenomyomata of the uterine horn or Fallopian tube. 4. Adenomyomata of the round ligament. 5. Uterine mucosa in the ovary. 6. Adenomyomata of the utero-ovarian ligament.

7. Adenomyomata of the utero-sacral ligament. 8. Adenomyomata of the sigmoid flexure. 9. Adenomyomata of the rectus muscle. 10. Adenomyomata of the umbilicus."

Dr. Cullen after giving briefly the clinical picture and histological findings in cases of adenomyomata of the body of the uterus reported a remarkable case. The right horn of a bicornate uterus was the seat of a widespread and diffuse adenomyoma, the right tube contained a pregnancy, the left tube was the seat of an adenomyoma, and the left ovary had been converted into a large retention cyst.

Adenomyoma of the Rectovaginal Septum.—Dr. Cullen laid unusual emphasis on this group of cases and pointed out that many had in the past undoubtedly been overlooked. If left alone the patient in time becomes a chronic invalid or dies as a result of the disease. The clinical picture in adenomyoma of the rectovaginal septum is typical. In the early stages the patient comes complaining of much pain just before or at the beginning of the period and especially on defecation. On bimanual examination a small nodule is felt directly behind the cervix. It cannot at this stage be confused with any other lesion.

Cullen then reported in detail and illustrated ten new cases of adenomyoma of the rectovaginal septum that he had recently personally observed.

Adenomyoma of the Uterine Horn or Fallopian Tube.—These growths were next considered and the speaker reported a case in which the tube was 1 cm. in diameter and solid. It consisted of typical adenomyoma.

Adenomyoma of the Round Ligament.—Cullen recorded the first case of this variety in the JOHNS HOPKINS HOSPITAL BULLETIN for 1896 and has had several since then. In his most recent paper he refers to a case in which a discrete adenomyoma was found in the round ligament about 2 cm. from the uterine cornua. It contained quantities of typical uterine mucosa.

Uterine Mucosa in the Ovary.—Cases published by W. W. Russell, Charles Norris, Dewitt B. Casler and others were discussed, and Cullen referred to some recent cases he had observed in which uterine mucosa was found in the ovary. This abnormal position of uterine mucosa may lead to most unusual clinical symptoms as noted in Casler's case.

Adenomyomata of the utero-ovarian ligament are of little clinical significance and are recognized only at operation or in the laboratory.

Adenomyomata of the uterosacral ligament are very infrequent and are small. Cullen reported a case that recently came under his care. He diagnosed the condition at operation, removed the adenomyoma and then brought the ends of the uterosacral ligament together again.

Adenomyomata of the Sigmoid Flexure.—Cullen records the case of a young woman who had an advanced adenomyoma of the rectovaginal septum. At operation a puckered tumor was found partially encircling the sigmoid near the pelvic brim. It looked like a cancer. On histological examination it proved to be an adenomyoma. The condition is extremely rare. Cuthbert Lockyer could find the record of only one similar case, that reported by Robert Meyer.

Adenomyoma in the Left Rectus Muscle.—Cullen reports a case that had come under the care of Dr. William F. Shallenberger of Atlanta, Ga. An adenomyoma 1.5 x 2.5 cm. was found in the lower end of the left rectus. It presented the typical picture of adenomyoma.

Adenomyoma of the Umbilicus.—Cullen briefly mentions this group of tumors and refers the reader to his chapter on this subject in his book on the umbilicus.

Brief Summary.—Adenomyomata consisting of a matrix, of non-striped muscle and fibrous tissue with typical uterine mucosa scattered throughout it are to be found in the uterus, rectovaginal septum, tubes, round ligaments, utero-ovarian ligaments, uterosacral ligaments, sigmoid flexure, rectus muscle and umbilicus. Moreover, we occasionally find large quantities of normal uterine mucosa in the ovary. Adenomyomata form one of the most interesting groups of tumors that we have to deal with in the female pelvis.

The paper is of such a nature that it cannot be satisfactorily abstracted. It is accompanied by about fifty original illustrations.

DISCUSSION

DR. RICHARDSON.—Every one, I am sure, who is interested in the development of gynecological surgery feels under obligations to Dr. Cullen for having, through his splendid work on adenomyomata, contributed so much of scientific as well as of practical value towards a better understanding of this group of cases about which we formerly knew so little. It has been my good fortune to have seen three cases of adenomyoma of the recto-vaginal septum, and there are one or two clinical points in connection with them which should be emphasized. The first is that the presenting symptom in all of my cases was dysmenorrhœa, a complaint commonly regarded as of secondary importance. But these cases teach us that adenomyoma should be carefully searched for in every case of severe and intractable dysmenorrhœa. My first case was encountered some ten years ago when very little was known about this neoplasm and I did not know the exact nature of the pelvic pathology. The tumor began in the anterior wall of the rectum just back of the cervix and presented all of the characteristics of a small inflammatory area. Conservative surgical measures were employed but, in spite of these, the condition developed progressively and fairly rapidly until it produced a state of chronic invalidism. After some months an effort was made to alleviate the suffering by a hysterectomy and at the operation I found, in addition to the somewhat enlarged uterus, a diffuse distribution throughout the pelvis of a similar inflammatory-looking process formerly seen at its beginning in the anterior rectal wall. The effect of this new growth was absolutely to immobilize the lower portion of the uterus, the broad ligaments and the rectum as if they had been encased in cement. Removal of the uterus was disappointing both as regards inhibition of the process and relief of symptoms. Some months later I was

forced to perform a radical resection of the rectum under tremendous technical difficulties, which resulted in death from surgical shock.

In my other two cases the growth was situated just behind the cervix but had also involved the anterior rectal wall below the peritoneum or culdesac of Douglas. Resection of the rectum in this location is a serious and difficult operation. I decided to advise the use of radium first and if this fails, to resect the bowel before the growth becomes extensive. If operation becomes necessary, as it probably will, preliminary panhysterectomy, as suggested by Dr. Cullen, is the method of choice.

Adenomyoma of the rectovaginal septum is, therefore, a very serious condition; one, indeed, that must be regarded at least as semi-malignant, and which, if let alone, will eventually lead to chronic invalidism and death.

Dr. Emil Novak.—There are one or two points which I should like to hear Dr. Cullen discuss. In the first place, I have been struck with the relationship which appears to exist between adenomyoma of the uterus and the condition known as hyperplasia of the endometrium. The latter, it may be noted, was also first described by Dr. Cullen, as far back as 1900. In many cases of adenomyoma of the uterus, the mucous membrane, both of the surface of the uterus, and also deep down in the muscular tissue, shows the characteristic pattern of hyperplasia. Even from a clinical point of view these two conditions—hyperplasia and adenomyoma—seem to be related. Both are characterized by excessive menstruation. I have observed a number of cases in which curettage, perhaps repeated several time, has yielded a typical hyperplastic endometrium, and in which subsequent removal of the uterus showed it to be the seat of an unsuspected adenomyoma. The apparent connection between the two conditions suggests various interesting possibilities. Hyperplasia, as the term indicates, is characterized by a genuine increase in both the epithelial and stromal elements of the endometrium. Adenomyoma, in a broad sense, is characterized by a hyperplasia of the muscular elements. Perhaps both conditions are produced by the same underlying cause.

There has been considerable discussion as to the etiology of adenomyoma, especially in the recent German literature. Most of the German authors are inclined to believe that the condition is of inflammatory origin. For example, in a recent article, adenomyoma of the rectovaginal septum is spoken of as adeno-serositis. As regards adenomyoma in general, there seems little ground for this inflammatory theory. While inflammation may cause gland proliferation, it can scarcely explain why the glands in adenomyoma are commonly surrounded by a well-marked mantle of normal endometrial stroma.

I mention these facts merely in an effort to lure Dr. Cullen into a discussion of the cause of this interesting lesion.

Dr. Cullen.—The first case Dr. Richardson referred to was a most interesting one. I saw this patient and on opening the abdomen found a uterus about twice the natural size and studded with small myomata. The posterior part of the cervix was firmly adherent to the rectum, and on separation of the two, a raw surface at least 2 to 2.5 cm. in diameter was left on the anterior surface of the rectum. Under ordinary circumstances I would have done a hysterectomy at once, but this patient had recently become engaged and I did not feel at liberty to adopt so radical a procedure without further watching the case. Moreover, at that time we knew absolutely nothing about adenomyoma of the rectovaginal septum.

As you have heard from Dr. Richardson this patient went from bad to worse and finally he had to remove a portion of the rectum.

The development in the adenomyoma in some cases seems to be slow, in others very rapid and the pelvis in time becomes choked with the growth.

Adenomyomata of the rectovaginal septum are at times almost impossible to remove. In one of our cases the ureters ran directly through the adenomyoma. At each period they were markedly constricted, were dilated above the point of obstruction and there was pain in both renal regions due to the damming back of urine. In that case I tunneled the ureters out of the growth, lifted them up and attached them loosely to the sides of the pelvis.

Where it was impossible to remove the entire adenomyoma radium seemed to keep it in check, in at least once instance.

Hyperplasia of the endometrium is a well-defined clinical entity and is a very frequent cause of prolonged and profuse menstrual periods. The histological picture of the endometrium is characteristic. The mucous membrane is thicker than usual. The surface epithelium is intact. Some of the glands are small and round, others large, round or irregular. The gland epithelium is thicker than usual. The stroma is much denser than normal, due to the large increase in the number of stroma cells, and in the nuclei of these cells one frequently finds nuclear figures. The histological picture is definite and cannot be confused with any other pathological condition of the endometrium.

The cause of adenomyoma is unknown. There is no evidence that it is due to an inflammation, as has been suggested by some authorities. The islands of uterine mucosa in the adenomyoma pour out their quota of menstrual blood at the period. This cannot escape; it causes tension in the tumor and undoubtedly irritation, which seems to stimulate further growth.

2. Paroxysmal Auricular Fibrillation. Dr. Verne R. Mason.

Published in the May, 1920, number of the Bulletin, page 145.

DISCUSSION

Dr. Hamman.—There is hardly any clinical condition more dramatic and more interesting than paroxysms of auricular fibrillation. I have observed the condition frequently and yet, whenever I meet it again, this astonishing derangement of cardiac mechanism excites endless wonder and fascination.

I have encountered it especially in two groups of cases. The first group consists of patients past forty years of age with hypertension or myocardial disease. Paroxysms of fibrillation occur with especial frequency at the period when the earliest symptoms of myocardial insufficiency come on and sometimes the advent of fibrillation precipitates the symptoms of myocardial insufficiency. The paroxysms may last from a minute or two to several days or longer. Between the paroxysms the heart may show no evidence of disease or, if hypertension be present, only the changes associated with the high blood pressure. I have seen a number of elderly patients fibrillate transiently during minor disorders such as attacks of diarrhea, and after a number of such transient paroxysms occurring over a period of years finally develop permanent fibrillation.

The second group is made up of otherwise young adults many of them robust and vigorous. The paroxysms of fibrillation come on without any determinable cause and last a varying length of time. Between the attacks the most rigorous examination fails to reveal any cardiac abnormality. After a number of attacks the heart usually fibrillates permanently although it may then continue to fibrillate for years without the development of any symptoms of myocardial insufficiency.

Paroxysms of fibrillation occur in association with other conditions of which perhaps the most important and interesting is disease of the thyroid gland. Although there is little note of it in the literature fibrillation frequently occurs in the late stages of thyroid disease. Permanent fibrillation is sometimes preceded by paroxysms of fibrillation. I have recently observed an interesting instance. The patient complained of attacks of palpitation. Examination revealed the classical symptoms of a large adenoma of the thyroid. I thought the attacks of palpitation were due to attacks of sinus tachycardia until the patient presented herself during an attack when it was obvious that the auricles were fibrillating. The patient refused operation because I was unwilling to promise that removal of the thyroid would prevent the occurrence of further attacks.

DR. CARTER.—Not the least interesting fact in connection with auricular fibrillation is that in spite of all our knowledge of the condition, we really know little concerning the actual cause of the onset of the attack.

In spite of the theories advanced by Rothberger and Winterberg, by Lewis and by Garrey, in explanation of the pathological physiology, that it is due either to a tachysystole, associated with conspicuous shortening in the refractory period of the auricular muscle, or to multiple foci of stimulation, or to the existence of multiple areas of block, no one of these views explains satisfactorily the fundamental cause of the onset of the disturbance, particularly in the transient or paroxysmal form.

In the light of these cases reported by Dr. Mason, and of some of those found in the literature, are we not perhaps justified in believing, from the standpoint of the etiology of its onset, that clinical auricular fibrillation may be divided into two distinct groups, as has been suggested by Robinson, the one associated with evidence of gross pathological change, the other with changes in the blood supply or in the subtler chemical reactions taking place within the myocardium and not necessarily dependent upon structural change.

The instances of transient or paroxysmal fibrillation occurring in the course of an infection and such cases as those reported by Robinson, following hydrogen sulphide poisoning, would fall into the latter group, while those cases occurring in the presence of myocardial and vascular changes, in many of which hypertonus is a conspicuous feature, would fall into the former; though it would be difficult to deny the influence of metabolic changes in these cases also.

Even more difficult to explain satisfactorily are those rare instances of fibrillation occurring in patients under 40 years of age, which remain permanently established, with no evidence of myocardial changes beyond a slight ventricular hypertrophy with a normal cardiac response to effort and with absolutely no symptoms of cardiac distress on the part of the individual. Through the kindness of Dr. Thayer, I have recently seen such an instance in a man of 32, in whom fibrillation had been permanently established for 14 months.

In Dr. Mason's series the age incidence has been high, above 45 or 50, which is what one would expect. In the series reported by Krumbaar, there was one instance of transient fibrillation in a young man of 18.

It is to be hoped that with the advances in our knowledge of cardiac pathological physiology, the elucidation of the etiological factor, especially in relation to these transient and paroxysmal cases, may be cleared up.

MARCH 15, 1920

1. Cinematograph: Cases of Lethargic Encephalitis. DR. HENRY M. THOMAS.

2. Lethargic Encephalitis. Poliomyelitis and Australian X-Disease. (Abstract.) DR. SIMON FLEXNER.

The world has recently passed through or is now passing through epidemics of at least two diseases, the main effects of which are exerted on the central nervous organs. They are poliomyelitis and lethargic encephalitis. In addition, an epidemic affection of the central nervous system has recently been reported from Australia differing in certain respects from both these affections and which for the time being is denominated X-disease. It is my purpose to speak to you of these several diseases and especially to enable you to compare their pathology with one another by means of a series of lantern pictures to be thrown on the screen. It has fortunately been a simple matter to obtain material in this country for lantern slides from cases of poliomyelitis and even from cases of lethargic encephalitis; and I am indebted to Doctor J. B. Cleland of Sydney, Australia, for specimens from the X-disease. Moreover, I have obtained through the British Medical Research Committee specimens from the early cases of lethargic encephalitis arising in England. I am thus enabled to bring together for your observation examples of the

several kinds of epidemic nervous diseases mentioned as they arose in the United States, England and Australia.

In presenting the subject of this lecture to you, I wish to lay stress on the fact that these epidemics of nervous affections are very remarkable, both by reason of their magnitude and their kind, and thus to arouse an interest which through enlarging knowledge may make us safer from their ravages.

It is now clear that the frightful explosion of poliomyelitis which centered in New York State in 1916 can be traced to a series of small outbreaks of the disease in Norway and Sweden that culminated in the relatively severe epidemic of 1905; on the basis of the study of this epidemic Wickman issued his epoch-making book in 1907. It was doubtless this Scandinavian epidemic of 1905 which led to the pandemic of 1906-1907 that spread over Europe, crossed the Atlantic to America, gradually extended over North America, and then passed to South America and the Orient, since which time the disease has prevailed to some extent in the United States and elsewhere every summer and autumn.

Poliomyelitis, even in some degree of epidemicity, was, however, known in the United States previous to 1907. The largest single recorded outbreak prior to 1907 is the epidemic occurring in Vermont in 1894 and reported by Caverly. We get a good notion of the difference between the situation in 1894 and that in 1916 by recalling that the Vermont epidemic included less than 200 cases, whereas in New York State alone in 1916 the recorded cases numbered more than 20,000.

So much, then, for epidemic poliomyelitis by way of introduction to our main theme—lethargic encephalitis. We have seen that it is possible to trace the source of an epidemic or pandemic wave of a given disease. Epidemic poliomyelitis was indeed known in the United States prior to 1907, but no great or widespread epidemic outbreak had ever occurred in this country before that date.

The circumstances are quite different with respect to lethargic encephalitis. There is no history of outbreaks of that affection prior to the present so-called epidemic. Here again, however, by following chronologically the occurrence of the disease in other countries, we can trace the connection of the cases arising in the United States with certain cases which were first recognized in Vienna in the winter of 1916. Moreover, it is now possible to follow the spreading wave of the disease by way of France and England (in which countries cases were recognized in 1918) to the United States where the first cases appeared toward the end of 1918 and in the early months of 1919.

There is now no doubt that the disease which von Economo studied in Vienna in 1916 and to which he gave the name lethargic encephalitis, is identical with the disease to which we are applying that name at the present time. It is now merely of historical interest to recall that both in Austria and in England the disease was misinterpreted and attributed to food poisoning, *i. e.*, botulism, with which condition it has in common the paralysis of the eye muscles. A histological study of the central nervous system of fatal cases in Austria first, then in England and France, later in the United States and now in many other countries, has brought out profound distinctions from botulism, and provided a pathological-histological basis for the symptomatic and pathological complex now embraced under the denomination of lethargic or epidemic encephalitis.

Of course, the facts regarding the outbreak of 1916 in Vienna were delayed in reaching Western Europe and the United States because of war conditions. Indeed the disease itself, in spite of all barriers, penetrated into England and France in advance of the literature concerning it. But the essential point at present is to recognize that in the United States and doubtless in other western lands an epidemic disease of sinister nature is prevailing for the first time. We are therefore confronted with a condition of present menace and one also of safe-guarding the future so as to prevent, if possible, the establishment of permanent foci in this country.

I said that there is no history of a previous outbreak of encephalitis lethargica in the United States. This does not mean that cases of encephalitis had not been observed before. The point is important since it happens that encephalitis is not an infrequent sequel to epidemic influenza. Because of this association, the question has been raised in various quarters whether after all lethargic encephalitis is not merely a form of post-influenzal encephalitis. I believe that the question can be answered negatively. First, the Viennese outbreak in 1916 antedated the influenza epidemic. Next, no such frequent association of encephalitis with influenza epidemics had been previously noted. Finally, there are pathological differences in the brain in cases of frank post-influenzal encephalitis and cases of lethargic encephalitis, which should not be overlooked. My contention is that for the present and until indubitable evidence is adduced to uphold the notion of a dependent relation of lethargic encephalitis to epidemic influenza, the former should be regarded as an independent disease of infectious and in some degree communicable nature.

I said above that the frequent association of encephalitis with influenza had not been noted in previous epidemics of influenza. This, in my opinion, is a correct statement, it being understood that the word "frequency" has reference to the occurrence of scores and even of hundreds of cases such as have been reported in recent months in the United States alone—and, of course, only a fraction of the cases arising are thus reported or even, possibly, identified. It is a matter of some importance to have this fact quite clearly in one's mind, because in tracing backward the history of affections with which lethargic encephalitis may possibly be identified, two instances are frequently quoted—one dating from 1712 and relating to an outbreak of so-called "sleeping sickness" centering about Tübingen in Germany, and the other dating from 1890-1892 and relating to a semi-mysterious disease called "nona" said to have occurred about the borders of Austria and Italy. In both these periods epidemic influenza was raging; hence the suggested connection of one with the other.

On the other hand, it is impossible to form any adequate notion whatever of the nature of the so-called "nona" or indeed to become convinced that a form of "sleeping sickness" actually prevailed at that time in the region mentioned. The references in print are nearly all in the lay press of the day, not in the medical press. Moreover, it is clear that other countries equally attacked by the epidemic influenza of 1889-1892 did not show an unusual number of severe cases of encephalitis.

Accepting for the present that lethargic encephalitis is a clinical entity we may next inquire as to the pathological conditions which signalize it.* The characteristic appearances are found in the brain and chiefly in the grey matter at the base; they consist of perivascular and interstitial cellular invasions associated with edema and occasional hemorrhages, the latter small and frequently microscopic. The cellular accumulations are mononuclear—made up of lymphocytes, plasma cells and polyblasts with, at times, proliferated glia cells. The lesions seek the grey matter and are most abundant and pronounced about the third ventricle and the Sylvian aqueduct, but they involve the large nuclei below the lateral ventricle, the optic thalamus, the pons and medulla, and even, in some degree, the spinal cord, especially in the cervical part. The cortex is somewhat, but less, affected. The relation of the nuclei of the third, fourth and sixth nerves to the third ventricle and Sylvian aqueduct accounts for the frequency of paralysis of the ocular muscles.

A comparison of the lesions in poliomyelitis and in encephalitis lethargica bring out four essential facts of difference: (1) The location is dissimilar; in poliomyelitis the spinal cord, medulla and pons suffer most. The grey matter located further anteriorly usually escapes and the cortex is infrequently involved. (2) While lymphocytes, plasma cells and even polyblasts occur in the lesions in poliomyelitis, the polymorphonuclear leucocyte plays a more prominent part than in encephalitis. (3) The meninges are far more infiltrated with cells in poliomyelitis, which probably explains the greater changes present in that condition in the cerebrospinal fluid. (4) Finally, in poliomyelitis neuronophagocytosis, in the spinal cord especially, is a very common phenomenon, whereas in encephalitis it is met with only infrequently.

We have therefore in poliomyelitis and lethargic encephalitis two definite pathological conditions affecting chiefly the brain and spinal cord with which the symptoms in each instance can be correlated. The two diseases are obviously distinct pathologically, and as experiment has shown, are distinguishable etiologically. Poliomyelitis is readily transmissible to monkeys through inoculation with the affected central nervous tissues; lethargic encephalitis is either not transmissible at all or only rarely and with difficulty.

There is a third epidemic disease of the central nervous organs of which our information is recent and, at the moment, rather meagre. But it is of great interest to ascertain whether this third disease belongs to one or the other category we have been discussing, or is an independent affection. The point is not merely academic. It is a serious enough circumstance to have two severe and highly fatal epidemic diseases of the central nervous system flourishing extensively at the present time. We should be cautious therefore before adding to the list of these enemies of mankind.

This third affection comes to us under the name of Australian X-disease. It has been described in detail by Doctor J. B. Cleland * who has kindly sent me tissues from fatal cases in man and from inoculated animals. It prevailed in parts of New South Wales, Victoria and Queensland in 1917 and 1918 and was highly fatal. Several hundred cases were reported. At first the disease was regarded as epidemic poliomyelitis, but most of the cases did not show the usual spinal cord involvement, and few instances of typical and frank flaccid paralysis of the extremities were noted. The age distribution of cases resembles that of poliomyelitis; the mortality (70 per cent) is far higher than in that disease, but the seasonal incidence is the same—namely, late summer and early autumn (the month period being, of course, reversed in the southern hemisphere) while lethargic encephalitis has thus far prevailed in the winter period.

The pathological changes in the spinal cord in Australian X-disease resemble those of epidemic poliomyelitis. Cellular infiltration of blood vessels, of the interstitial tissues and neuronophagocytosis are striking. The monkey is readily infected by inoculation with the affected nervous organs of man. So far, then, there is similarity between Australian X-disease and poliomyelitis. But whereas no one has succeeded in communicating poliomyelitis to sheep, calves and the horse by inoculation, Cleland believes that he has infected those animals with Australian X-disease. This is a very important distinction; and this ready communicability of Australian X-disease to animals distinguishes it not only from poliomyelitis but notably also from encephalitis.

I have been enabled, as I said, to study tissues from Australian X-disease in man, monkey, sheep, calf and horse. The lesions in the nervous tissues in man and the monkey are similar to those of poliomyelitis in man and monkey. There is no analogy in poliomyelitis with the lesions in the other animals. Brain tissues, not spinal cord of the other animals, were sent me by Doctor Cleland. They show mononuclear cell invasion of the meninges and focally of blood vessels in the cortex, and a certain extrusion of similar cells in the grey matter about the affected vessels. The evidences then of a meningoencephalitis of mononuclear variety are convincing.

There is one question which might be raised regarding the results of the experimental inoculations, namely, whether in the infection of the sheep, calf and horse (the inoculations were made from the infected monkeys) a second and extrane-

* All the points mentioned in connection with the pathological histology were illustrated with lantern slides.

* Cleland, J. B., and Campbell, A. W., Acute encephalo-myelitis. A clinical and experimental investigation of an Australian epidemic., *Brit. Med. Jour.*, May 31, 1919, page 663.

ous pathogenic microorganism might have been accidentally introduced. I do not emphasize this point, which is to be regarded as a mere possibility, in the endeavor to correlate the findings in Australia with those elsewhere in the world and to exercise due caution and restraint before accepting as certain the existence of a third active epidemic disease of the central nervous system. There are other ways to approach this matter in the effort to clear up the subject, namely, through cross inoculation tests in recovered monkeys with poliomyelitis material, serum immunization experiments, etc. All this will doubtless be attempted in time.

To conclude: I regard epidemic poliomyelitis as a disease with a special pathologic anatomical foundation in the central nervous organs and a specific inciting microorganism. I regard as probable that lethargic encephalitis will be found to occupy a similar special category; while I am inclined to reserve judgment respecting Australian X-disease, which I think may possibly be discovered to be a somewhat special instance of epidemic poliomeylitis in which the brain rather than the spinal cord has had to stand the greater shock of attack.

DISCUSSION

Dr. Barker.—I would like to ask whether, as we look back with the knowledge we now have of the disease, enough has been discovered about it to permit us, if we were starting over again in 1907, to prevent its development? Is there any lesson to be drawn concerning the prevalence of lethargic encephalitis?

Dr. Flexner.—Dr. Barker's question is not an easy one to answer. No one, I think, can say just what might have happened had we, that is, the medical profession in general, been better informed regarding epidemic poliomyelitis in 1907. Wickman's remarkable book, based on the Swedish epidemic of 1905, appeared in German in 1907. He decribed the abortive type of case and laid on it great stress as a factor in disseminating the disease. Knowledge and appreciation of this fact were slow in making progress in this country. It is a matter of some national pride that actually Caverly first apprehended the abortive type of poliomyelitis during the Vermont epidemic of 1894.

Let us suppose for the moment that Wickman's book had become widely known in 1907 and the next subsequent years, that the medical profession had been alert about the abortive cases, and especially that suitable and adequate measures of control had been applied. It is by no means certain, of course, that the later outbreaks of poliomyelitis would have been certainly prevented; it is equally by no means certain that their extent and severity might not have been mitigated. In questioning the value of general preventive measures, we are of course putting on trial some of the most common of our public health procedures to limit the spread of the infectious diseases communicated by personal contact. Until other and more direct means of control are secured, we are still dependent on measures based on personal hygiene to combat a whole group of communicable diseases and especially those in which the mode of infection is by way of the upper respiratory mucous membrane, among which poliomyelitis is to be placed and not improbably lethargic encephalitis also.

NOTES ON NEW BOOKS

The Blind. By Harvey Best. Cloth, $4.00. (*New York: The Macmillan Company, 1919.*)

In this monumental work by Dr. Harvey Best, Professor of Sociology at the University of Kentucky, two important subjects are fully dealt with—the prevention of blindness and the economic condition of the blind.

Approximately 64 per cent, or nearly two-thirds, of the blindness in the United States, so the author estimates, is preventable. Of specific diseases of the eye likely to cause blindness, the most important are, in the order of their seriousness, cataract, atrophy of the optic nerve, glaucoma, ophthalmia neonatorum, trachoma, and corneal ulcer. Of these diseases, ophthalmia neonatorum and trachoma are under ready control, the disease being preventable in babies by means of the Credé method. To fight trachoma, seven hospitals have been established in the country—three in Kentucky, and one each in Virginia, Tennessee, West Virginia, and North Dakota. Two other infectious eye diseases, keratitis and conjunctivitis, may be checked by comparatively simple precautions. As for the large amount of blindness which is a concomitant of old age, or that which arises from apparently unavoidable diseases, there would be a substantial lessening if good lighting arrangements and saner modes of life were adopted.

Diseases other than specific affections of the eye cause 9.2 per cent of all blindness, the greatest offenders being, in order, measles, meningitis, scarlet fever, smallpox, typhoid fever, and influenza. In these cases careful attention and isolation will reduce the incidence of blindness.

Accidents especially from explosives cause 13.5 per cent of blindness. Almost all of these may be prevented by care and proper safeguards, such as goggles for men working at dangerous operations in factories and contrivances like guards on emery wheels and exhaust systems to carry off dust and sharp particles in factories.

Although, according to Best's statistics, 46 per cent of blindness cannot be definitely accounted for, being reported as congenital or due to catarrh, colds, or sore or strained eyes, most of these cases also, too, seem to be preventable, since apparently they are largely due to diseases mentioned above.

As for the economic condition of the blind, statistics from census reports seem to show that only about 6.6 per cent are able to make an independent living, four-fifths of those gainfully employed earning a sum below $500, nearly two-thirds below $300, more than one-half below $200 and nearly one-third below $100, many being subsidized by what are known as pensions, which amount to an average maximum of $250 a year. It is no wonder, then, that the cost of blindness amounts to the enormous sum of $30,725,000 yearly.

The question now arises, "Cannot the blind be so trained that most of them may be able to make an independent livelihood?"

The first essential to such an end is that the public should be aroused to the possibilities of blind labor. Instead of looking on the blind man as helpless, instead of taking the pencil-selling beggar as the type, the public must realize that the blind man wants opportunity, not sympathy or charity.

The second essential is that the blind man should be properly and thoroughly trained in an industrial, commercial or professional occupation. In this connection, a paragraph from "Charities and the Commons" is interesting, although not entirely fair:

"Many of the States have been generous in their provision for the education of the young blind. . . . . At the close of the school period of their lives, however, at the most critical juncture, when their whole future is to be determined, intelligent interest seems suddenly to cease. . . . . (the blind) have outgrown the school and we have no place for them in the active world. . . . . They have no business training. Many of them have no profession, most of them have no trade."

The most salient fact with reference to the welfare of the blind is that their opportunities for vocational training are limited. Yet of all classes they need such training the most. To provide it, there are only the workshop and summer sessions in a few of the schools for youth. There is no higher institution of an exclusively educational nature open to blind adults, where they may be trained, as they must be, if they are to be capable workers in trade, industry, or profession.

Add to this fact the further fact that about half the blind children of the country, between the ages of five and nineteen, are not attending any school, and one needs not wonder why the blind man is looked upon as incapable. The fault for such poor attendance does not lie with the schools, because workers for the blind are more than zealous in urging parents to send their children to school. The fault rather lies in the fact that compulsory education laws are not rigidly enforced.

Throughout the book Mr. Best evinces thorough study and careful analysis of his material. He began the work in 1908, finishing in 1919, after examining hundreds of books, pamphlets, manuscripts, reports, statutes, and letters. His work is authoritative and appears at a critical time when interest in the blind and in the possibilities of labor for the handicapped is at its highest flood.

The several bibliographies are comprehensive, thorough and up to date.

J. B., JR.

Manual of Psychiatry. Edited by AARON J. ROSANOFF, M. D., Clinical Director, King's Park State Hospital, N. Y., Lieutenant Colonel, Officers' Section, Medical Reserve Corps, U. S. Army. Fifth edition. Revised and enlarged. Cloth. 684 pages. (*New York: John Wiley & Sons, Inc. London: Chapman & Hall, Limited, 1920.*)

The fifth edition of de Fursac's Manual of Psychiatry appears now as Manual of Psychiatry, edited by Rosanoff, with de Fursac, Rosanoff, Hollingworth, Miss Jarrett and Neymann as contributors. It is no longer merely the French rendering of German psychiatry with some American annotations. The annotations have become a more and more important part of the book and they consist not only of numerous new chapters, but of many transformations of the original. Rosanoff has incorporated Neymann's technique of the spinal fluid study, Meyer's outline of aphasia study, the development of the child, the Terman revision of the Binet-Simon scale (including the average and the superior adult), Kent-Rosanoff's free association test with the frequency-tables and a grouping of the results, group tests, the classification of mental diseases adopted by the American Medico-Psychological Association, with G. H. Kirby's definitions and explanatory notes—altogether a very valuable collection of information. The 120 pages on the practice of psychiatry give a very valuable summary of the methods in use in modern American psychiatry.

Constitutional disorders, alcoholic, drug and syphilitic disorders and miscellaneous groups supply the nosological headings.

Cerebral arteriosclerosis appears as Chapter XV under "Syphilitic Disorders."

In the discussion of the psychoneuroses, Rosanoff gives considerable attention to the war experience.

The student will find the book of considerable help for reviews and for reference.

The Principles of Anatomy as Seen in the Hand. By FREDERIC WOOD JONES, D. Sc., M. B., B. S. Cloth, $5.00 net. (*Philadelphia: P. Blakiston's Son & Co., 1920.*)

This is that rare thing, a continuously readable book on gross anatomy,—interesting because it deals with ideas instead of cataloging bare facts, and none the less instructive because those principles which the author has chosen for exposition are in some part not those which awake most attention in our schools.

It is to be hoped that the newer methods now at work in our dissecting rooms may at length give us American publications of this type, which will show those who know gross anatomy only through the older text-books what stores of interest and utility there are in the anatomy of function as studied by the three methods of embryology, histogenesis, and especially physiology. A fourth source of aid in rationalizing the vastly numerous details of human structure, comparative anatomy, most of us have esteemed less valuable for teaching and practice, but of late we have seen our British colleagues make clever use of it. One Australian comparative anatomist (W. Colin M'Kenzie) has made even so seemingly remote a subject as the musculature of the marsupials do him good service as the foundation of practice in military orthopedics and of an illuminating work on "The Action of Muscles."

In "The Principles of Anatomy as Seen in the Hand" F. Wood Jones has likewise undertaken to show us how the details of structure may be made living and useful by comparison with other species and by a study of the gross physiology. His clear and lively teaching of anatomy from these aspects is founded upon sure knowledge; it is only when lessons are to be drawn from general physiology and embryology that the text wanes in vigor.

The opening chapters deal with the bones of the hand and wrist in a manner far more interesting than this subject traditionally assumes. In the chapter upon "Flexure Lines" there is solid information and also some good scientific jesting when the author examines the lore of palmistry in the light of comparative anatomy. A chapter on the fascias is a triumph of common sense, which every dissector should read as an antidote to the usual text-book description of fascias as square-edged walls of sheet-iron texture. The accounts of the general action of muscles and the position of rest are also sound applications of gross physiology, teaching the structures as they work, not merely as they look.

The chapters on the morphology and the detailed actions of the muscles are the surest of the book, for here the author is upon the ground of his own researches, and has much to teach the clinician and the anatomist. The student may be dismayed to find the subject of muscle-actions, as presented here, far more intricate than in the text-books, but he will also find it, for once, a live subject worth the exercise of good cortical substance, no longer a mere test of memory.

Much space is given to the thesis already enthusiastically expounded in an earlier book of the author ("Arboreal Man"),

that the fore-limb of man is not, as anatomists long taught and theologians repeated, the result of high specialization, but that, on the contrary, it retains to an astonishing degree the generalized structure of the vertebrate type. When the limb is specialized, its freedom is lost, as in the human foot and the fore-limbs of the hoofed mammals. Retention of versatile simplicity, with greater control, gives man his adaptable fore-limb, according to the thought-provoking notion of our author.

Discussions of the nerves of the hand, of the hand as a sense-organ, and of the relations of hand and brain, are careful and clear, but less original than the foregoing parts of the book. In the chapter on the vascular channels the author seems least at home, for he has not grasped the opportunity to base his account upon the principles of vascular development, which embryological studies have brought out in recent years. A brief discussion of generalities about the lymphatic system rests dogmatically upon one side of this actively controverted question. It is surely unsafe to think of the lymphatic ducts as phylogenetically earlier than the blood-vessels.

The book is written throughout in a very clear and easy style. There are numerous historical allusions and quotations, many of them from out-of-the-way sources, which are appropriately used in the interest of lucidity.

G. W. C.

Introduction to General Physiology. By W. M. Bayliss, M. A., D. Sc., F. R. S. Cloth, $2.50 net. (*London: Longmans, Green & Co., 1919.*)

Those who are already acquainted with Bayliss' contributions to the science of physiology will be ready to accept this small book without explanation. It is designed primarily, as the title indicates, for first studies of the subject and is a worthy successor to its forerunners written by Huxley and Martin.

The style is simple and succinct, with frequent helpful analogies to facilitate comprehension of the problems under discussion. The opening chapter surveys the newer work in physics and chemistry which has exerted so profound an influence on modern physiology. Then follow chapters on the several functional processes of the body considered from the standpoint of mammalian physiology. At the end of the book a series of experiments, correlated with the text, is given, which are adapted to laboratory exercises. Throughout the text frequent reference is made to the author's " Principles of General Physiology," thus providing access to a wider discussion for those who desire it.

The book should prove of very great value to those who are responsible for elementary courses in physiology. To others, and particularly to physicians who have of necessity lost touch with the later developments in the laboratory subjects, it will prove a pleasant means for review of the salient facts as seen by one of the most eminent physiologists of the day.

D. H.

BOOKS RECEIVED

John Coakley Lettsom and the Foundation of the Medical Society. Being the Presidential Address Delivered Before the Medical Society of London on October 8, 1917, by Sir St. Clair Thomson, M. D., F. R. C. P. Lond., F. R. C. S. Eng. 1918. 8°. 63 pages. Harrison & Sons, London.

The Rockefeller Foundation. Review for 1918. Public Health in Many Lands. Centers of Medical Education. War Relief and Welfare of American Troops. By George E. Vincent. 1919. 8°. 40 pages. New York.

The Rockefeller Foundation. China Medical Board. Third Annual Report January 1, 1917–December 31, 1917. 1918. 8°. 29 pages. New York, N. Y.

Smithsonian Institution. Annual Report of the Board of Regents Showing the Operations, Expenditures, and Condition of the Institution for the Year Ending June 30, 1915. 1916. 8°. 544 pages. Government Printing Office, Washington.

Industrial Nursing. For Industrial, Public Health, and Pupil Nurses, and for Employers of Labor. By Florence Swift Wright, R. N. 1919. 12°. 179 pages. The Macmillan Company, New York.

Cerebrospinal Fluid in Health and in Disease. By Abraham Levinson, B. S., M. D. With a foreword by Ludvig Hektoen, M. D. With fifty-six illustrations, including five color plates. 1919. 8°. 231 pages. C. V. Mosby Company, St. Louis.

Psychiatric-Neurologic Examination Methods. With Special Reference to the Significance of Signs and Symptoms. By Dr. August Wimmer. Authorized translation by Andrew W. Hoisholt, M. D. 1919. 8°. 177 pages. C. V. Mosby Company, St. Louis.

Collected Papers from The Research Laboratory Parke, Davis & Co., Detroit, Mich. Dr. E. M. Houghton, Director. Reprints. Volume 6. 1919. 8°. 303 pages.

Connecticut State Medical Society. Proceedings of the 127th Annual Convention. Editor James Frederick Rogers. 1919. 8°. 296 pages. Published by the Society, New Haven, Connecticut.

Metropolitan Asylums Board. Annual Report for the year 1918. (21st year of issue.) 1919. 8°. 64 pages. Henderson & Spalding, Ltd., London.

Plastic Surgery, its Principles and Practice. By John Staige Davis, Ph. B., M. D., F. A. C. S. With 864 illustrations containing 1637 figures. 1919. 8°. 770 pages. P. Blakiston's Son & Co., Philadelphia.

American-Hellenic Society. Reports of the American Red Cross Commissions upon their activities in Macedonia, Thrace, Bulgaria, the Ægean Islands and Greece 1919. 8°. 30 pages. Published by permission of the American Red Cross for the American-Hellenic Society, by The Oxford University Press, American Branch, New York City.

State of Iowa. Eleventh Biennial Report of the Board of Control of Institutions for the period ending June 30, 1918. 8°. 354 pages. Published by the State of Iowa, Des Moines.

The Medical Treatment of Cancer. By L. Duncan Bulkley, A. M., M. D. 1919. 12°. 386 pages. F. A. Davis Company, Philadelphia.

Atlas of Operative Gynæcology. By Barton Cooke Hirst, M. D. 164 plates; 46 figures. 1919. 4°. 292 pages. J. B. Lippincott Company, Philadelphia and London.

Vicious Circles in Disease. By Jamieson B. Hurry, M. A., M. D. (Cantab.). With illustrations. Third and enlarged edition. 1919. 8°. 377 pages. P. Blakiston's Son & Co., Philadelphia.

Modern Dentistry for the Laity. Industrial Dentistry for the Corporation, Modern Preventive Dentistry and Industrial Welfare Dentistry. By Alfred A. Croker. Second edition. 1919. 12°. 136 pages. The Dental Register, Cincinnati, Ohio.

Thoughts of a Psychiatrist on the War and After. By William A. White, M. D. 1919. 12°. 137 pages. Paul B. Hoeber, New York.

Half a Century of Small-Pox and Vaccination. Being the Milroy Lectures delivered before the Royal College of Physicians of London on March 13, 18 and 20, 1919. By John C. McVail, M. D., LL. D. 1919. 8°. 86 pages. E. & S. Livingstone, Edinburgh.

Organization of Public Health Nursing. By Annie M. Brainard. 1919. 12°. 144 pages. The Macmillan Company, New York.

The Exact Diagnosis of Latent Cancer. An Enquiry into the True Significance of the Morphological Changes in the Blood. By O. C. Gruner, M. D. 1919. 8°. 79 pages. P. Blakiston's Son & Co., Philadelphia.

Report of the Scientific Work of the Surgical Staff of the Woman's Hospital in the State of New York. Edited by George Gray Ward, Jr., M. D., F. A. C. S. Volume II. 1919. 8°. 234 pages.

The Proceedings of the Charaka Club. Volume V. 1919. 8°. 101 pages. Paul B. Hoeber, New York.

The Venereal Diseases. An Outline of Their Management, Prepared Under the Surgeon General of the Army for the Use of Medical Officers. Revised for the use of civilian physicians. Third edition. Printed for the United States Public Health Service, Rupert Blue, Surgeon General. 1919. 24°. 159 pages. American Medical Association, Chicago.

Bacteriology in Abstract. By A. B. Wallgren, B. S., M. D. 1919. 24°. 340 pages. Medical Abstract Publishing Company, Pittsburgh, Pa.

A Text-Book of Human Physiology. Including a Section on Physiologic Apparatus. By Albert P. Brubaker, A. M., M. D., LL. D. Sixth edition, revised and enlarged with 356 illustrations. 1919. 8°. 794 pages. P. Blakiston's Son & Co., Philadelphia.

A Text-Book Upon the Pathogenic Bacteria and Protozoa. For Students of Medicine and Physicians. By Joseph McFarland, M. D., Sc. D. Ninth edition, revised with 330 illustrations, a number in colors. 1919. 8°. 858 pages. W. B. Saunders Company, Philadelphia and London.

College of Physicians of Philadelphia. Transactions. Third Series. Volume the Fortieth, 1918. 8°. 308 pages. Printed for the College, Philadelphia.

Yearbook of the United States Department of Agriculture, 1918. 8°. 760 pages. 1919. Government Printing Office, Washington.

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Bulletin of Iowa Institutions. (Under the Board of Control.) Published Quarterly. Volume XX. 1918. 8°. 261 pages.

The Carnegie Foundation for the Advancement of Teaching. Justice and the Poor. By Reginald Heber Smith. Bulletin Number Thirteen. 1919. 8°. 271 pages. New York City.

Carnegie Endowment for International Peace. Founded December Fourteenth, Nineteen Hundred and Ten. Year Book. No. 8. 1919. 8°. 209 pages. Washington, D. C.

Quarterly Medical Clinics. A Series of Consecutive Clinical Demonstrations and Lectures. By Frank Smithies, M. D. Volume I. Number 2. April, 1919. 8°. Medicine and Surgery Publishing Company, Inc., St. Louis.

Publications of the South African Institute for Medical Research. Edited by W. Watkins-Pitchford, M. D. (Lond.) No. XII. Observations and Experimental Investigations in Epidemic Influenza. By F. S. Lister, M. R. C. S., L. B. C. P., and E. Taylor, M. D. (G. W. Univ., U. S. A.) 1919. 8°. 23 pages. Hortors, Limited, Johannesburg.

Pellagra. By H. F. Harris, M. D. 1919. 8°. 421 pages. The Macmillan Company, New York.

Experimental Pharmacology. By Hugh McGuigan, Ph. D., M. D. Illustrated with 56 engravings and 7 colored plates. 1919. 8°. 251 pages. Lea & Febiger, Philadelphia and New York.

The Prevention of Dental Caries and Oral Sepsis. By H. P. Pickerill, M. D. Second edition. 1919. 8°. 374 pages. Paul B. Hoeber, New York.

Nervous and Mental Diseases. By Archibald Church, M. D., and Frederick Peterson, M. D. Ninth edition, thoroughly revised. With 350 illustrations. 1919. 8°. 949 pages. W. B. Saunders Company, Philadelphia and London.

Manual of Obstetrics. By Edward P. Davis, A. M., M. D., F. A. C. S. Second edition, revised. 1919. 12°. 478 pages. W. B. Saunders Company, Philadelphia and London.

Spanish Tales. For Beginners. Edited with notes and vocabulary by Elijah Clarence Hills, Ph. D., Litt. D. Revised edition with direct method exercises. 1919. 16°. 298 pages. Henry Holt and Company, New York.

Oxford Medical Publications. Publishers: Henry Frowde, London; Hodder & Stoughton, London. The following 10 volumes:

The Medical and Surgical Aspects of Aviation. By H. Graeme Anderson, M. B., Ch. B., F. R. C. S. With chapters on *Applied Physiology of Aviation.* By Martin Flack, M. A., M. B., and *The Acro-Neuroses of War Pilots.* By Oliver H. Gotch, M. B., Ch. B., M. R. C. P. (London) and an introduction by the Right Hon. Weir, of Eastwood, P. C. 1919. 8°. 255 pages.

Trench Fever, a Louse-Borne Disease. By Major W. Byam, R. A. M. C.; Captains J. H. Carroll, U. S. R., J. H. Churchill, R. A. M. C. (T.), Lyn Dimond, R. A. M. C., V. E. Sorapure, R. A. M. C., R. M. Wilson, R. A. M. C., and L. L. Lloyd, R. A. M. C. (T.). With an introduction by Lieut.-General Sir T. H. Goodwin, K. C. B. A foreword by Major-General Sir David Bruce, K. C. B., F. R. S., A. M. S., and a summary of the report of the American Trench Fever Commission by Lieut. R. H. Vercoe, R. A. M. C. 1919. 8°. 196 pages.

The Nervous Heart, Its Nature, Causation, Prognosis and Treatment. By R. M. Wilson, Captain, R. A. M. C., and John H. Carroll, Major, M. C., U. S. A. 1919. 16°. 136 pages.

Psychoses of the War, Including Neurasthenia and Shell Shock. By H. C. Marr, Lt.-Col., R. A. M. C. (Temp.). 1919. 8°. 292 pages.

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